

SUMMARY of PRODUCT CHARACTERISTICS

1. NAME OF HUMAN MEDICINAL PRODUCT

EVASIF® 245 mg Film Coated Tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Effective Substance:

Contains 300 mg tenofovir disoproxil fumarate, equivalent to 245 mg tenofovir disoproxil

Excipients:

Lactose monohydrate..... 164,80 mg
Croscarmellose sodium.....19,50 mg

For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Film-coated Tablets
Blue-colored, almond-shaped film coated tablets.

4. CLINICAL CHARACTERISTICS

4.1. Therapeutical indications

Evasif is indicated for use in the treatment of chronic hepatitis B infection in adults.

This indication is based on histological, virological, biochemical and serological responses in adult patients with HBeAg positive or HBeAg negative chronic hepatitis B, with compensated liver function and active viral replication, high serum alanine aminotransferase levels (ALT) or histologically active disease, who are nucleoside-naïve or nucleoside-experienced.

Evasif is used in the treatment of adults over 18 years of age, who are infected with HIV-1 in combination with other antiretroviral drugs.

In the demonstration of benefits of Evasif, the results of a study, on treatment-naïve patients including patients with high viral load (> 100,000 copies/ml), and studies, in which Evasif was added to the regular treatment (generally a triple therapy) on patients, who have shown early virological failure (< 10,000 copies/ml, in most patients < 5,000 copies/ml).

When deciding for a new regime for patients, for whom antiretroviral regime has failed, the forms of mutations related to different medicinal products and the treatment history of patients must be considered.

When appropriate, resistance test must be conducted.

4.2. Posology and method of administration

Treatment must be initiated by a physician, who is experienced in the treatment of chronic hepatitis B and/or HIV infection.

In exceptional cases, patients, who have difficulty swallowing, may take the drug after dissolving in at least 100 ml water, orange juice or grape juice.

Adults:

Recommended dose for chronic hepatitis B or HIV treatment is one tablet, taken per day with or without food.

Chronic hepatitis B: In case of loss of HBsAg or HBsAg seroconversion, tenofovir disoproxil fumarate treatment may be discontinued and on the other hand, optimal treatment duration is not known (see, Section 4.4).

Additional information for special populations:

Renal failure: Tenofovir is excreted through kidneys and in patients with renal failure, tenofovir exposure increases (see, Sections 4.4 and 5.2). Limited data from clinical studies support the administration of once-a-day tenofovir disoproxil fumarate to patients with mild renal failure (creatinine clearance 50-80 ml/min). In all patients with creatinine clearance < 50 ml/min, as explained below in detail, dose range adjustment is necessary.

Below, dose range adjustment guidelines for this population are based on the modeling of single-dose pharmacokinetic data in patients, who are not infected with HIV and hepatitis B virus with varying levels of renal failure, including end stage renal disease, requiring hemodialysis and may not be optimal. Therefore, in these patients, clinical response to therapy, and renal function must be closely monitored (see, Section 4.4).

	Creatinine clearance (ml/min)*			Hemodialysis patients
	50-80	30-49	10-29	
Recommended Tenofovir Disoproxil 245 mg Dose Range	Every 24 hours one tablet (no adjustment necessary)	Every 48 hours one tablet	Every 72-96 hours one tablet	After conclusion of hemodialysis session, one tablet every 7 days**

* Calculated using ideal body weight.

** In general, considering that there are three hemodialysis sessions, taking 4 hours in a week, one dose after cumulative hemodialysis time of 12 hours.

No dose suggestions have been established for patients with creatinine clearance less than 10 ml/min and who do not receive hemodialysis.

Hepatic failure: In patients with hepatic failure, clinically relevant pharmacokinetic changes have not been observed. Therefore in patients with liver failure, no dose adjustment is required (see, Section 5.2).

In case EVASIF is discontinued in patients with chronic hepatitis B, with or without HIV co-infection, the patients must be closely monitored for signs of deterioration of hepatitis (see. Section 4.4).

In children and adolescents up to 18 years of age: Efficacy and safety of EVASIF has not been established in patients below 18 years of age. Section 4.4). Until provision of further data, demonstrating efficacy and safety of tenofovir disoproxil fumarate in patients below 18 years of age, EVASIF must not be used in children and in adolescents up to 18 years of age.

Elderly: There is no data to make a dose recommendation for patients over 65 years of age (see. Section 4.4).

4.3. Contraindications

EVASIF is contraindicated for persons with hypersensitivity to effective substance and any of the excipients.

4.4. Special warnings and special precautions for use

Before commencement of tenofovir disoproxil fumarate treatment, HIV antibody test must be suggested to all patients, infected with Hepatitis B (see. HIV-1 and hepatitis B co-infection).

EVASIF must not be taken in combination with another pharmaceutical, containing tenofovir disoproxil fumarate.

Tenofovir disoproxil fumarate must not be administered in combination with adefovir dipivoxil.

Tenofovir disoproxil fumarate has not been studied in patients below 18 years of age.

Renal function: Tenofovir is excreted primarily through kidneys. In clinical practice renal failure, renal insufficiency, high creatinine, hypophosphatemia and proximal tubulopathy (including Fanconi syndrome) have been reported with tenofovir disoproxil fumarate use (see. Section 4.8).

Creatinine clearance must be calculated in all patients prior to initiation of tenofovir disoproxil fumarate treatment and it is recommended to monitor renal functions (creatinine clearance and serum phosphate) every four weeks in the first year and then every three months. In patients with the risk of renal failure, attention must be paid to more frequent monitoring of renal function.

In patients with moderate or severe renal failure, receiving daily doses of tenofovir disoproxil fumarate (creatinine clearance < 50 ml/min), exposure to tenofovir may increase and in these patients, dose range adjustment is necessary (see, Sections 4.2 and 5.2). Efficacy and safety of tenofovir disoproxil fumarate has not been established in patients with moderate or severe renal failure and therefore possible benefits of tenofovir disoproxil fumarate treatment must be assessed versus the risk of renal toxicity. In patients with prior renal failure, after commencement of tenofovir disoproxil fumarate treatment with long dose intervals, viral load changes, in addition to toxicity symptoms, such as deterioration in renal functions, must be closely monitored.

In case, in any patient, receiving tenofovir disoproxil fumarate, serum phosphate level is < 1.5 mg/dl (0.48 mmol/l) or creatinine clearance is < 50 ml/min, renal functions, including blood glucose levels, potassium in blood and urine glycosuria levels must be assessed within one week (see. Section 4.8 Proximal tubulopathy). In case creatinine clearance drops to < 50 ml/min, dose range of tenofovir disoproxil fumarate must be adjusted (see. Section 4.2). In patients with creatinine clearance below 50 ml/min or serum phosphate level below 1.0 mg/dl, suspending treatment with tenofovir disoproxil fumarate must be considered.

In patients, who have used recently or are using concomitantly nephrotoxic drugs (e.g., aminoglycosides, amphotericin B, foscarnet, ganciclovir, pentamidine, vancomycin, cidofovir or interleukin 2), use of tenofovir disoproxil fumarate must be avoided. In case concomitant use of tenofovir disoproxil fumarate and nephrotoxic agents can not be avoided, renal functions must be monitored every week.

In patients, using drugs, secreted by the same transporter, for example, secreted by human organic anion transporter 1 (hOAT1) (e.g., cidofovir, known as a nephrotoxic drug), tenofovir disoproxil fumarate has not been clinically assessed. This renal transporter (hOAT1) may be responsible for tubular secretion and partially renal elimination of tenofovir and cidofovir. Consequently, when administered concomitantly, the pharmacokinetics of these drugs may change. Unless absolutely necessary, the concomitant use of these drugs are not recommended, yet in case concomitant use is inevitable, renal functions must be monitored on a daily basis (see. Section 4.5).

Bone effects: In a 144-week controlled clinical study, comparing lamivudine and efavirenz with stavudine and tenofovir disoproxil fumarate in combination on antiretroviral treatment-naïve patients, infected with HIV, minor decreases have been observed in both treatment groups in hip and spinal bone mineral density. The decreases in bone mineral density of spine and the changes in bone biomarkers compared to baseline, are significantly greater in tenofovir disoproxil fumarate treatment arm in week 144. The decreases in bone mineral density of hip, are significantly greater in this treatment arm up to week 96. However, after week 144, fracture risk has not increased with respect to related bone anomalies. In case bone anomalies are suspected, appropriate consultation must be provided.

Resistance: In patients with antiretroviral experience, infected with HIV strains, having isolates with K65R mutation, use of tenofovir disoproxil fumarate must be avoided (see. Section 5.1).

Elderly patients: Tenofovir disoproxil fumarate has not been studied in patients over 65 years of age. A decrease in renal functions of the elderly patients, is possible, therefore, caution must be exercised when treating elderly patients with tenofovir disoproxil fumarate.

Liver disease: Tenofovir and tenofovir disoproxil fumarate are not metabolized by liver enzymes.

Deterioration of hepatitis after termination of therapy: Termination of hepatitis B treatment, including tenofovir disoproxil fumarate, may be associated with severe acute hepatitis exacerbations. Patients, infected with hepatitis B virus, who have discontinued tenofovir disoproxil fumarate, must be closely monitored for at least several months after the termination of treatment both with respect to clinical and laboratory follow-up. If appropriate, it may be necessary to restart hepatitis B treatment. In patients with advanced liver disease or

cirrhosis, deterioration of hepatitis following treatment may cause hepatic decompensation and therefore discontinuance of treatment is not recommended.

Co-Infection with Hepatitis C or D: There is no data concerning efficacy of tenofovir in patients, co-infected with hepatitis C or D virus.

HIV-1 and hepatitis B co-infection: tenofovir disoproxil fumarate must only be used as part of an appropriate antiretroviral combination regime due to the risk of development of resistance by HIV in patients, who are co-infected with HIV and hepatitis B.

Lactic acidosis: Lactic acidosis, generally related to hepatosteatorrhea, has been reported in connection with the use of nucleoside analogues. Preclinical and clinical data suggest that as a class effect of nucleoside analogues, the risk of lactic acidosis for tenofovir disoproxil fumarate was low. However, since tenofovir is structurally related to nucleoside analogues, this risk may not be ignored. Early symptoms (symptomatic hyperlactatemia) include benign digestive symptoms (nausea, vomiting and abdominal pain), non-specific malaise, loss of appetite, weight loss, respiratory symptoms (rapid and/or deep breaths) or neurological symptoms (including motor weakness). Mortality rate of lactic acidosis is high and may be related to pancreatitis, liver failure or renal failure. Lactic acidosis generally develops several months into treatment.

In case of symptomatic hyperlactatemia and metabolic/lactic acidosis, progressive hepatomegaly or increased aminotransferase levels, treatment with nucleoside analogues must be terminated.

Caution must be exercised when administering nucleoside analogues to patients with hepatomegaly, hepatitis or other known risk factors for liver disease and hepatosteatorrhea (several medical products, including alcohol associated cases), and in particular obese women. In patients, co-infected with hepatitis C and treated with alpha interferon and ribavirin, there may also be a risk.

High-risk patients must be closely monitored.

In patients, infected with HIV, combination antiretroviral therapy has been associated with redistribution of body fat (lipodystrophy). Long-term consequences of these events are not currently known. Information concerning the mechanism of this phenomenon is insufficient. It has been hypothesized that there was a connection between visceral lipomatosis with protease inhibitors and lipodystrophy with nucleoside reverse transcriptase inhibitors. Higher risk of lipodystrophy has been associated with individual factors, such as advanced age, and drug-dependent factors, such as long-term antiretroviral therapy and metabolic disorders. Clinical examination must include an assessment, related to physical symptoms of redistribution of fat. Attention must be paid to measurement of fasting serum lipids and blood glucose. Lipid disorders must be treated in a clinically appropriate manner (see. Section 4.8).

Tenofovir is structurally related to nucleoside analogues and therefore lipodystrophy risk may not be ignored. However, 144-week clinical data, provided from antiretroviral treatment-naïve patients, infected with HIV, have shown that the risk of lipodystrophy was lower with tenofovir disoproxil fumarate compared to stavudine, when administered in combination with lamivudine and efavirenz.

It has been shown that nucleoside and nucleotide analogues caused varying levels of mitochondrial damage in vitro and in vivo. In HIV-negative infants, who are exposed to nucleoside analogues in utero and/or post-natal, mitochondrial function disorder has been reported. Principal reported adverse effects are hematological (anemia, neutropenia) and metabolic (hyperlactatemia, hyperlipazemia) disorders. These effects are mostly transient. Some late-onset neurological disorders (hypertonia, convulsions, abnormal behavior) have been reported. It is currently unknown whether the neurological disorders are temporary or permanent. Clinical and laboratory follow-ups must be performed for all children, even HIV-negative children, who have been exposed to nucleoside and nucleotide analogues in utero and in case of observation of related symptoms, they must be fully examined for mitochondrial dysfunction. Findings do not affect the existing antiretroviral treatment usage guidelines in pregnant women for prevention of vertical transmission of HIV.

Immune Reactivation Syndrome: During the initial stages of combined antiretroviral therapy (CART), in patients with HIV infection, who have severe immune deficiency, an inflammatory reaction may develop against the asymptomatic or residual opportunistic pathogens and may cause severe clinical conditions or exacerbation of symptoms. Typically, these reactions have been observed within the first few weeks or months after the start of treatment (CART). Examples, related to these include cytomegalovirus retinitis, general and/or focal mycobacterium infections and *Pneumocystis carinii* pneumonia. All inflammatory symptoms must be considered and when necessary, treatment must be initiated.

Osteonecrosis: Although it is thought that the etiology is multi-factorial (including corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index), osteonecrosis cases have been reported in particular in patients with advanced HIV disease and/or prolonged exposure to combined antiretroviral treatment (CART). Patients must be recommended to seek medical attention in case of pain and ache in joints, stiffness or difficulty of movement.

Concomitant administration of tenofovir disoproxil fumarate and didanosine, is not recommended. Concomitant administration of tenofovir disoproxil fumarate and didanosine, results in a 40 to 60 % increase in systemic exposure to didanosine, which may increase the risk of didanosine-related adverse events (see, Section 4.5). Rare pancreatitis and lactic acidosis cases, which may sometimes be fatal, have been reported. Concomitant administration of tenofovir disoproxil fumarate and 400 mg daily didanosine, has been associated with significant decrease in CD4 cell count, possibly due to an intracellular interaction, increasing phosphorylated (that is, active) didanosine. Reduced 250 mg didanosine dosage, applied with tenofovir disoproxil fumarate treatment, has been associated with high rates of virological failure within the framework of several tested combinations.

Triple nucleoside treatment: tenofovir disoproxil fumarate, when combined with lamivudine and abakavir in the form of the single daily dose regime, and also with lamivudine and didanosine, it has been reported that high level of virological insufficiency and early onset resistance developed in HIV patients.

The patients must be notified that it was not proven that tenofovir disoproxil fumarate eliminated the risk of infecting other persons with HIV or hepatitis B virus through sexual intercourse or blood contamination. Appropriate measures must be maintained.

EVASIF contains lactose monohydrate. Consequently, patients with rare hereditary galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption problems, must not take this pharmaceutical.

This medicinal product contains less than 1 mmol (23 mg) sodium in each film coated tablet; at these doses, no side effects are expected.

4.5. Interactions with other medicinal products and other forms of interaction

Based on the results of in vitro tests and the known elimination routes of tenofovir, CYP450 interaction potential with other products, involving tenofovir, is low.

Tenofovir is excreted through kidneys both via filtration and active secretion via anionic transporter (hOAT1). Concomitant administration of other medicinal products, actively secreted from anionic transporter (e.g., cidofovir) and tenofovir disoproxil fumarate, may increase the concentrations of tenofovir or concomitant medicinal product (see. Section 4.4).

Use in combination with antiviral products

The administration of emtricitabine, lamivudine, entecavir, indinavir and efavirenz in combination with tenofovir disoproxil fumarate has not caused any interaction.

When tenofovir disoproxil fumarate is administered in combination with lopinavir/ritonavir, no changes have been observed in the pharmacokinetics of lopinavir and ritonavir. When tenofovir disoproxil fumarate is administered in combination with lopinavir/ritonavir, tenofovir AUC has increased approximately by 30 %. Higher tenofovir concentrations could exacerbate tenofovir-related adverse events, including kidney diseases.

When enteric coated capsules of didanosine are administered 2 hours before or together with tenofovir disoproxil fumarate, didanosine AUC has increased by an average of 48 % and 60 % respectively. When buffered tablets are administered 1 hour prior to tenofovir, average increase in didanosine AUC is 44 %. In both cases, pharmacokinetic parameters for tenofovir, given with a light meal, have not changed. **Concomitant administration of tenofovir disoproxil fumarate and didanosine, is not recommended** (see. Section 4.4).

When tenofovir disoproxil fumarate is administered concomitantly with atazanavir, a decrease has been observed in atazanavir concentrations (compared to atazanavir 400 mg, a decrease in AUC and C_{min} by 25 % and 40 % respectively). When ritonavir was added to atazanavir, while the negative effect on C_{min} had significantly decreased, the decrease in AUC was at the same level (compared to atazanavir/ritonavir 300/100 mg AUC and C_{min} decreases by 25 % and 26 % respectively). Concomitant administration of atazanavir/ritonavir with tenofovir has resulted in an increase in tenofovir exposure. Higher tenofovir concentrations could exacerbate tenofovir-related adverse events, including kidney diseases. Combination administration of atazanavir with tenofovir together with ritonavir, has been made in a clinical study.

Other interactions

The administration of tenofovir disoproxil fumarate, with methadone, ribavirin, rifampicin (see, Section 4.4) or hormonal contraceptive norgestimate and ethinyl estradiol has not caused any pharmacokinetic interactions.

When administered together with combination product emtricitabine/tenofovir disoproxil fumarate, pharmacokinetics of tacrolimus have not changed. When administered alone or in combination with tacrolimus, no clinically significant changes were seen in the pharmacokinetic parameters of tenofovir.

4.6. Pregnancy and lactation

General recommendation

Pregnancy category: B

Women with childbearing potential (Contraception)

There is no clinical data concerning pregnant women, who are exposed to tenofovir disoproxil fumarate.

Animal studies do not indicate harmful effects of tenofovir disoproxil fumarate directly or indirectly with respect to pregnancy, embryonic/fetal development, parturition or postnatal development (see. Section 5.3).

Considering that possible risks for developing human fetuses are not known, tenofovir disoproxil fumarate must be used in women with childbearing potential, together with effective contraception.

Pregnancy

tenofovir disoproxil fumarate must only be used during pregnancy in case necessary and in case the benefits outweigh the possible risks against the fetus.

Lactation

In animal studies, it has been shown that tenofovir was excreted in breastmilk. It is not known whether tenofovir is excreted in human breastmilk. Therefore, it is recommended that the mothers, treated with tenofovir disoproxil fumarate should not breastfeed their infants.

As a general rule in order to avoid infection of the infant with HIV or hepatitis B virus, the women, infected with HIV and hepatitis B, must not breastfeed their babies under any conditions.

Fertility

In rats, no effects on mating or fertility, were found.

4.7. Effects on ability to drive vehicles and operate machinery

No studies concerning effect on driving vehicles and operating machinery have been made. However, the patients must be informed that dizziness is reported during tenofovir disoproxil fumarate treatment.

4.8. Undesired effects

The adverse effects, given below, relate to the clinical studies and post-marketing experience, involving HIV and HBV patients. Frequencies are described as very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $\leq 1/100$), rare ($\geq 1/10,000$ to $\leq 1/1,000$), or very rare ($\leq 1/10,000$) including "unknown reports." Since some events are voluntarily reported out of a population of an unknown size, it may not be possible to make frequency estimates at all times.

• HIV-1:

The assessment of undesired effects has been based on two studies, conducted on 653 treatment-experienced patients, treated with tenofovir disoproxil fumarate (n=443) or placebo (n=210) for 24 weeks, in combination with other antiretroviral drugs, and in addition, a

double-blind, comparative, controlled study, in which treatment-experienced 600 patients were given lamivudine and efavirenz in combination with 245 mg tenofovir disoproxil fumarate (n=299) or stavudine (n=301) for a term of 144 weeks.

Approximately one-third of the patients is expected to experience undesired effects following tenofovir disoproxil fumarate treatment, in combination with other antiretroviral agents. Generally, these reactions were mild or moderate gastrointestinal events.

Undesired effects, whose relationship with the treatment is suspected (at least possible), are listed below with respect to body-system-organ class and frequency.

Nervous system disorders:

Very common: dizziness

Gastrointestinal diseases:

Very common: diarrhea, nausea, vomiting

Common: gas

Approximately 1 % of patients, treated with tenofovir disoproxil fumarate, have discontinued treatment due to gastrointestinal events.

Combination antiretroviral therapy is associated with metabolic anomalies, such as hypertriglyceridemia, hypercholesterolemia, insulin resistance, hyperglycemia and hyperlactatemia (see. Section 4.4).

Combination antiretroviral therapy in HIV patients is associated with redistribution of body fat (lipodystrophy) including peripheral and facial subcutaneous fat loss, intra-abdominal and visceral fat increase, breast hypertrophy and dorsocervical fat accumulation (buffalo hump).

In a 144-week controlled clinical study, comparing stavudine and tenofovir disoproxil fumarate in combination with lamivudine and efavirenz on antiretroviral treatment-naïve patients, patients, receiving tenofovir disoproxil fumarate have shown a smaller incidence of lipodystrophy compared to patients, receiving stavudine. Compared to comparative arm, tenofovir disoproxil fumarate arm has shown smaller, yet significant increases in triglyceride and total cholesterol.

During the start of combination antiretroviral therapy (CART), in patients, infected with HIV with severe immune deficiency, an inflammatory reaction against asymptomatic or residual opportunistic infections, may develop (see. Section 4.4).

In particular, as generally known risk factors, in patients with advanced HIV disease or prolonged exposure to combination antiretroviral therapy (CART), osteonecrosis cases have been reported. The frequency of the same is unknown (see, Section 4.4).

- **Hepatitis B:**

In the assessment of adverse reactions, the experience, provided from two double-blind, comparative, controlled studies, in which 641 patients with chronic hepatitis B and compensated liver disease, took 245 mg tenofovir disoproxil (as fumarate) (n=426) per day or 10 mg adefovir dipivoxil (n=215) per day for 48 weeks.

Adverse reactions, whose relationship with the treatment is suspected (at least possible), are listed below with respect to body-system-organ class and frequency.

Gastrointestinal diseases:

Common: nausea

- ***Post-marketing experience:***

In addition to adverse reaction reports, related to clinical studies, during post-approval use of tenofovir disoproxil fumarate, the following adverse reactions have been identified. Since these events are voluntarily reported out of a population of an unknown size, it may not be possible to make frequency estimates at all times.

Immune System Disorders:

Very rare: allergic reaction

Metabolism and nutrition disorders:

Very common: hypophosphatemia

Rare: lactic acidosis

Respiratory, thoracic, and mediastinal disorders:

Very rare: dyspnea

Gastrointestinal diseases:

Common: increase in amylase levels

Rare: pancreatitis

Very rare: stomach ache

Hepatobiliary disorders:

Rare: Elevation in liver enzymes (most frequently AST, ALT, GGT)

Very rare: hepatitis

Skin and subcutaneous disorders:

Rare: rash

Musculoskeletal and connective tissue disorders:

Unknown: myopathy, osteomalacia (both related to proximal renal tubulopathy)

Renal and urine tract conditions:

Rare: renal failure, acute renal failure, proximal tubulopathy (including Fanconi syndrome), increase in creatinine level, proteinuria, renal insufficiency.

Very rare: acute tubular necrosis, polyuria

Unknown: nephritis (including acute interstitial nephritis), nephrogenic diabetes insipidus.

General disorders and administration site conditions:

Very rare: asthenia

Reporting of Suspected Adverse Reactions

After authorization, reporting of suspected adverse reactions has great importance. Reporting allows continuous monitoring of benefit/risk balance of the pharmaceutical. Healthcare professionals must report any suspected adverse reaction to Turkish Pharmacovigilance Center (TÜFAM) (www.titck.gov.tr; e-mail: tufam@titck.gov.tr; tel: 0 800 314 00 08; fax: 0 312 218 35 99)

4.9. Overdose and Treatment

In case of an overdose, the patient must be monitored for symptoms of toxicity (see, Sections 4.8 and 5.3) and standard support treatment must be administered as required.

Tenofovir may be removed with hemodialysis; median hemodialysis clearance of tenofovir is 134 ml/min. Elimination of tenofovir with peritoneal dialysis has not been studied.

5. PHARMACOLOGICAL CHARACTERISTICS

5.1. Pharmacodynamic Properties

Pharmacotherapeutic group: Antiviral for systemic use, ATC-code: J05AF07

Effective substance Tenofovir disoproxil fumarate is the fumarate salt of prodrug tenofovir disoproxil. Tenofovir disoproxil is absorbed and is converted to tenofovir a nucleoside monophosphate (nucleotide) analogue. Then tenofovir at steady state is transformed to tenofovir diphosphate, which is a mandatory chain terminal with cellular enzymes, as a result of two phosphorylation reactions in activated T cells. Intracellular half-life of tenofovir diphosphate is 10 hours in activated peripheral blood mononuclear cells (PBMCs) and is 50 hours at steady state peripheral blood mononuclear cells. Tenofovir diphosphate directly competes with natural deoxyribonucleotide substrate for binding and inhibits viral polymerases and after entry to DNA, terminates DNA chain. Tenofovir diphosphate is a weak inhibitor of cellular polymerases α , β and γ . When compared to kinetic inhibition constant of tenofovir diphosphate against HIV-1 reverse transcriptase (K_i) (0.02 $\mu\text{mol/l}$) K_i value against human DNA polymerase α is 200 times greater (5.2 $\mu\text{mol/l}$), and K_i value against human polymerases β and γ is 3000 times greater (respectively 81.7 and 59.5 $\mu\text{mol/l}$). Tenofovir diphosphate with its 0.18 $\mu\text{mol/l}$ K_i value, inhibits HBV polymerase. Tenofovir at concentrations up to 300 $\mu\text{mol/l}$ has shown no effects on mitochondrial DNA synthesis or lactic acid production in in vitro determinations.

Tenofovir has in vitro antiviral activity against retroviruses and hepadnaviruses.

HIV-1: Tenofovir concentrations, required for 50 % inhibition of wild type laboratory strain of HIV-1_{IIIB} (IC_{50}) is 1-6 $\mu\text{mol/l}$ in lymphoid cell lines and is 1.1 $\mu\text{mol/l}$ against HIV-1 subtype B isolates in PBMCs. In addition, tenofovir is effective against HIV-1 subtypes A, C, D, E, F, G and O and against HIV_{BaL} in primary monocyte/macrophage cells. Tenofovir has in vitro activity against HIV-2 with an IC_{50} of 4.9 $\mu\text{mol/l}$ at MT-4 cells against HIV-2 and against Hepatitis B virus with an IC_{50} of 1.1 $\mu\text{mol/l}$ in HepG2 2.2.15 cells.

The activity of tenofovir against recombinant HIV-1, showing didanosine resistance (L74V), zalcitabine resistance (YT69D) and multinucleoside drug resistance (Q151M complex) mutations remains within the limit of two times IC_{50} for wild type. It is seen that the activity of tenofovir against HIV-1 helices and the mutations, related to zidovudine-associated

mutations, was dependent against the type and number of such resistance mutations. In case of T215Y mutation, it has been observed that IC_{50} increased twofold. In 10 samples with more than one mutations, associated with zidovudine (mean 3.4), it has been observed that IC_{50} increased by average 3.7 times (range: 0.8 to 8.4).

The susceptibility of T69S double addition multinucleoside resistant HIV-1 against tenofovir has not been decreased ($IC_{50}>10$ fold). Tenofovir shows full activity against HIV-1, resistant to non-nucleoside reverse transcriptase inhibitor with K103N or Y181C mutations. Due to different targeted viral enzymes, cross-resistance to protease inhibitor resistance mutations is not expected.

K65R mutation in HIV-1 strains and in reverse transcriptase whose susceptibility to tenofovir has been decreased by 3-4 times, has been determined in vitro. K65R mutation in reverse transcriptase may be chosen from zalcitabine, didanosine and abakavir and cause a decrease in susceptibility against zalcitabine, didanosine, abakavir and lamivudine (respectively 14, 4, 3 and 25 fold). In patients with antiretroviral experience, having isolates with K65R mutation, use of tenofovir disoproxil fumarate must be avoided (see. Section 4.4).

Hepatitis B Virus: In vitro activity of tenofovir against hepatitis B virus, has been assessed in HepG2.2.2.15 cell line. EC_{50} values for tenofovir are between 0.14 to 1.5 $\mu\text{mol/l}$. CC_{50} (50% cytotoxicity concentration) values are $> 100 \mu\text{mol/l}$. Tenofovir diphosphate with its 0.18 $\mu\text{mol/l}$ K_i value (inhibition constant) inhibits recombinant HBV polymerase. In in vitro pharmaceutical combination studies of nucleoside anti-hepatitis B virus reverse transcriptase inhibitors lamivudine, telbivudine and entecavir, together with tenofovir, additional anti-hepatitis B virus activity has been shown. With tenofovir and emtricitabine combination, mild contribution to synergistic action has been observed.

Clinical Efficacy in HIV-1: The efficacy of tenofovir disoproxil fumarate in adults with HIV-1 infection, who are treatment-experienced or treatment-naïve, has been shown with 48-week studies on adults, infected with HIV-1, who are treatment-experienced.

In GS-99-907 study, 550 patients with treatment experience have been treated with placebo or 245 mg tenofovir disoproxil (in the form of fumarate) for 24 months.

. Baseline mean CD4 cell count was 427 cell/mm³, baseline mean plasma HIV-1 RNA level 3.4 log₁₀ copy/ml (in 78 % of the patients, there is a viral load below 5,000 copies/ml) and previous HIV treatment duration is mean 5.4 years. Baseline genotypic analysis of HIV isolates, obtained from 253 patients, has shown that in 94 % of patients, there were HIV-1 resistance mutations, associated with nucleoside reverse transcriptase inhibitors, in 58 %, mutations, related to protease inhibitors and in 48 %, mutations, related to non-nucleoside transcriptase inhibitors.

In week 24, mean time-weighted change in log₁₀ plasma HIV-1 RNA levels compared to baseline (DAVG₂₄), was -0.03 log₁₀ copies/ml and -0.61 log₁₀ copies/ml for persons, receiving placebo and tenofovir disoproxil (as fumarate) ($p < 0.0001$). Patients, who have 3 or more mutations, related to thymidine analogue, comprising M41L or L210W reverse transcriptase mutation (TAM), have shown decreasing susceptibility to tenofovir disoproxil (as fumarate) treatment.

Virological response has significantly decreased in patients with viral isolates, bearing > 10 -fold zidovudine phenotypical resistance. For CD4 count, at week 24 (DAVG₂₄), a statistically significant change has been seen in favor of 245 mg tenofovir disoproxil fumarate in the time-weighted mean change compared to baseline (for 245 mg tenofovir disoproxil fumarate + 13

cell/mm³ versus for placebo -11 cell/mm³, p value = 0.0008). Antiviral response to tenofovir disoproxil fumarate has lasted for 48 weeks (DAVG₄₈ -0.57 log₁₀ copy/ml, the rate of patients with HIV-1 RNA level below 400 or 50 copies/ml is, respectively 41 % and 18 %). Eight patients, treated with 245 mg tenofovir disoproxil fumarate (2 %) have developed K65R mutations in the first 48 weeks.

144-week, double-blind active agent controlled phase of GS-99-903 study, in patients with HIV-1 infection, who are antiretroviral treatment-naïve, when used in combination with lamivudine and efavirenz, the efficacy and safety of 245 mg tenofovir disoproxil fumarate has been assessed against stavudine. Baseline mean CD4 cell count is 279 cell/mm³, baseline mean plasma HIV-1 RNA level is 4.91 log₁₀ copies/ml, in 19 % of patients, there is symptomatic HIV-1 infection and in 18 % of patients, there is AIDS. Patients have been grouped according to their baseline HIV-1 RNA and CD4 count. 43 % of the patients have a baseline viral load of > 100,000 copies/ml and CD4 count of 39 % is < 200 cells/ml.

According to intent-to-treat analysis (deficient data and change in antiretroviral treatment (ART) are considered as failure) in 48-week treatment the rate of patients with HIV-1 RNA levels below 400 copies/ml and 50 copies/ml was respectively 80 % and 76 % in 245 mg tenofovir disoproxil fumarate arm, these rates were 84 % and 80 % in stavudine arm. On week 144, the rate of patients with HIV-1 RNA levels below 400 copies/ml and 50 copies/ml, is 71 % and 68 % with 245 mg tenofovir disoproxil (as fumarate), it was 64 % and 63 % in stavudine arm.

In 48-week treatment, the mean change in HIV-1 RNA and CD4 count compared to baseline was similar in both treatment groups (in 245 mg tenofovir disoproxil fumarate and stavudine groups, respectively -3.09 log₁₀ and -3.09 log₁₀ copies/ml; +169 and +167 cells/mm³). In 144-week treatment, the mean change compared to baseline was similar in both treatment groups (in 245 mg tenofovir disoproxil fumarate and stavudine groups, respectively -3.07 log₁₀ and -3.03 log₁₀ copies/ml; +263 and +283 cells/mm³). Independently from HIV-1 RNA and CD4 counts, it was seen that a consistent response was provided with 245 mg tenofovir disoproxil fumarate treatment.

Patients in tenofovir disoproxil fumarate group have shown insignificantly higher levels of K65R mutations compared to active treatment group (2.7 % vs. 0.7 %). In all cases with K65R mutation, efavirenz or lamivudine resistance has existed prior to the formation of mutation or has emerged with the formation of resistance. In 245 mg tenofovir disoproxil (as fumarate) arm, eight patients had HIV, bearing K65R, the first of these has occurred in the first 48 weeks of treatment and the last in week 96. Until week 144, no other K65R mutations have been observed. From both phenotypical and genotypical analyses, no evidence, pointing that there were other ways of acquisition of resistance to tenofovir, has been provided.

Clinical efficacy in chronic hepatitis B: In display of the benefits of tenofovir disoproxil fumarate, histological, virological, biochemical and serological responses in patients, who have compensated liver condition, with HBeAG-positive and HBeAG-negative chronic hepatitis patients and in patients, who are co-infected with HIV-1 and hepatitis B virus, who show clinical evidence, pointing that previous treatment failed. In these clinical studies, in baseline, the patients have active viral replication. Tenofovir disoproxil fumarate has shown anti-hepatitis B activity in patients with hepatitis B virus, bearing mutations, related to lamivudine resistance.

Experience in patients with compensated liver condition In patients with compensated liver disease, the results, provided during 48 weeks, from two randomized, phase 3, double blind studies, comparing tenofovir disoproxil fumarate and adefovir dipivoxil, are given in the table below. GS-US-174-0103 study has been conducted on 266 HBeAg positive patients (randomized and treated) on the other hand GS-US-174-0102 study has been conducted on 375 HBeAg negative and HBeAg positive patients (randomized and treated).

In both of these studies, tenofovir disoproxil fumarate is significantly superior over adefovir dipivoxil with respect to full response efficacy endpoint (HBV DNA levels < 400 copies/ml and at least 2 point improvement in Knodell necroinflammatory score without deterioration in Knodell fibrosis). In addition, 245 mg tenofovir disoproxil (as fumarate) treatment, has been associated with significantly greater number of patients with HBV DNA levels < 400 copies/ml, when compared to adefovir dipivoxil 10 mg treatment. In both treatment with respect to histological response in week 48 (defined as a 2-point improvement in Knodell necroinflammatory score without deterioration in Knodell fibrosis) similar results have been provided (see. Table 1).

In GS-US-174-0103 study, at week 48, in tenofovir disoproxil fumarate group, there are significantly more patients with normalized ALT levels and have achieved HBsAg loss, compared to adefovir dipivoxil (see. Table 1).

Table 1. Efficacy parameters at week 48 in compensated HBeAg positive and HBeAg negative patients

	174-0102 Study (HBeAg Negative)		174-0103 Study (HBeAg Positive)	
Parameter	245 mg tenofovir disoproxil (as fumarate) n= 250	10 mg adefovir dipivoxil n= 125	245 mg tenofovir disoproxil (as fumarate) n= 176	10 mg adefovir dipivoxil n= 90
Complete Response (%)^a	71*	49	67*	12
Histology				
Histological Response (%) ^b	72	69	74	68
HBV DNA (%) < 400 copies/mL (< 69 IU/ml)	93*	63	76*	13
ALT (%) Normalized ALT^c	76	77	68*	54
Serology (%) HBeAg Loss/Seroconversion	not applicable	not applicable	22/21	18/18
HBsAg Loss/Seroconversion	0/0	0/0	3*/1	0/0

* versus adefovir dipivoxil $p < 0.05$, ^aComplete response is described as HBV DNA levels < 400 copies/ml and at least 2 point improvement in Knodell necroinflammatory score without deterioration in Knodell fibrosis, ^bat least 2 point improvement in Knodell necroinflammatory score without deterioration in Knodell fibrosis, ^cThe population, used in analysis of ALT normalization, only include patients, who have ALT levels exceeding ULN in baseline.

Tenofovir disoproxil fumarate, when compared to adefovir dipivoxil has been associated with significantly greater number of patients with undetectable HBV DNA levels (< 169 copies/ml [< 29 IU/ml]; Roche Cobas Taqman HBV assay measurement limit), (respectively GS-US-174-0102 study; 91 %, 56 % and GS-US-174-0103 study; 69%, 9%).

When GS-US-174-0102 and GS-US-174-0103 studies are combined, the response to Tenofovir disoproxil fumarate treatment between patients, who had baseline nucleoside experience (n=51) and who are nucleoside treatment naive (N=375) and with normal ALT (n=21) and abnormal ALT (n=405) was found to be comparable. 49 out of 51 patients with prior nucleoside experience, have been previously treated with lamivudine. 73 % of patients with nucleoside experience and 69 % of nucleoside naive patients, have achieved complete response with treatment; 90 % of nucleoside-naive patients and 88 % of nucleoside-experienced patients, have achieved a HBV DNA suppression of < 400 copies/ml. All patients with normal baseline ALT, and 88 % of patients with abnormal ALT have achieved DNA suppression of < 400 copies/ml.

In a randomized, double-blind, controlled 48-week 245 mg tenofovir disoproxil (as fumarate) study, conducted on patients, co-infected with HIV-1 and chronic hepatitis B (ACTG Study) mean baseline serum HBV DNA levels in patients, randomized to tenofovir arm is 9.45 log₁₀ copies/ml (n=27). 245 mg tenofovir disoproxil (as fumarate) treatment in patients with 48-week data (n=18), has been associated with a -5.74 log₁₀ copies/ml mean change in baseline serum HBV. In addition, at week 48, 61 % of the patients have normal ALT.

Experience from patients with persistent viral replication: The efficacy and safety of 245 mg tenofovir disoproxil (as fumarate) or 245 mg tenofovir disoproxil (as fumarate) plus 200 mg emtricitabine have been assessed in a randomized, double blind study (GS-US-174-0106 study) on HBeAg Positive and HBeAg negative patients with persistent viremia (HBV DNBA ≥ 1000 copies/ml), who have received 10 mg adefovir dipivoxil for a term of more than 24 weeks. On week 24, treatment with a regime comprising tenofovir has resulted in 77 % of patients, with HBV DNA < 400 copies/ml [< 69 IU/ml] (46/60) and in 62 % of patients (37/60) with undetectable HBV DNA (below 169 copies/ml [< 29 IU/ml] Roche Cobas TaqMan HBV assay limit). In addition, in week 24, the rate of patients with normal ALT is 68 %.

Clinical Resistance: 426 HBeAg negative (GS-US-174-0102, n=250) and HBeAg positive (GS-US-174-0103, n=176) patients have been assessed for genotypical changes in HBV polymerase. Genotypical assessments have been made on all patients with HBV DNA > 400 copies/ml at week 48. No mutations, associated with tenofovir disoproxil fumarate resistance have been identified.

Cross-Resistance: Cross resistance has been observed between hepatitis B virus reverse transcriptase inhibitors. In cell-based assays, hepatitis B virus strains, showing rtV173L, rtL180M and rtM204I/V mutations, associated with resistance to lamivudine and telbivudine, has shown a susceptibility to tenofovir, ranging between 0.7 times to 3.4 times of the wild type virus. Hepatitis B virus strains, showing rtL180M, rtT184G, rtS202G/I, rtM204V and

rtM250V mutations, associated with resistance to entecavir, has shown a susceptibility to tenofovir, ranging between 0.6 times to 6.9 times of the wild type virus. Hepatitis B virus strains, showing resistance mutations rtA181V and rtN236T, associated with adefovir has shown a susceptibility to tenofovir, ranging between 2.9 times to 10 times of the wild type virus. Viruses with rtA181T mutation have remained susceptible to tenofovir with EC50 values 1.5 times of wild-type virus.

5.2. Pharmacokinetic properties

General Properties

Tenofovir disoproxil fumarate is a water-soluble ester pro-drug, which transforms rapidly to tenofovir and formaldehyde in vitro.

Tenofovir transforms to tenofovir monophosphate and active component tenofovir diphosphate in the cell.

Absorption

In HIV-infected patients, after oral administration of tenofovir disoproxil fumarate, tenofovir disoproxil fumarate is rapidly absorbed and is transformed to tenofovir. Maximum tenofovir concentrations have been observed within 1 hour after the dose is administered in fasting conditions or two hours when administered after meals. In fasting conditions, the oral bioavailability of tenofovir in tenofovir disoproxil fumarate is approximately 25 %. A meal with high fat content has increased oral bioavailability with an increase in tenofovir AUC by approximately 40 % and C_{max} by approximately 14 %. Following the first dose of tenofovir disoproxil fumarate, plasma median C_{max} has ranged between 213 to 375 ng/ml.

Distribution

Following intravenous administration, it is estimated that the steady state distribution volume of tenofovir was approximately 800 ml/kg. After oral administration of tenofovir disoproxil fumarate, tenofovir is distributed to many tissues, such as kidneys, liver and intestinal contents at highest concentrations (pre-clinical studies). In the tenofovir concentration range of 0.01 to 25 µg/ml the rate of in vitro binding to plasma or serum proteins for tenofovir is lower than 0.7 % and 7.2 %, respectively.

Biotransformation

In vitro studies have shown that tenofovir disoproxil fumarate or tenofovir were not substrates for CYP450 enzymes. In addition, at concentrations, significantly higher than in vivo concentrations (approximately 300 times), tenofovir has not inhibited the in vitro drug mechanism, mediated by any one of human CYP450 isoforms (CYP3A4, CYP2D6, CYP2C9, CYP2E1 or CYP1A1/2).

Tenofovir disoproxil fumarate at a concentration of 100 µmol/l/1 has no effects on any CYP450 isoforms, with the exception of CYP1A1/2, where a small, yet statistically significant (6 %) decrease was observed in CYP1A1/2 substrate metabolism. Based on this data, observation of clinically significant interactions involving tenofovir disoproxil fumarate and medicinal products, metabolized by CYP450, is unlikely.

Elimination

Tenofovir is essentially excreted from kidneys both via filtration and effective tubular excretion; following intravenous administration, approximately 70 to 80 % of the dose, excreted in urine is unchanged. It is estimated that total clearance is approximately 230

ml/hour/kg (approximately 300 ml/min). It is estimated that the renal clearance was approximately 160 ml/hour/kg (approximately 210 mg/min) and is greater than glomerular filtration rate. This shows that tubular secretion was an important part of tenofovir elimination. After oral administration the terminal elimination half-life of tenofovir is 12 to 18 hours.

Elderly:

In elderly (65 years of age and over) pharmacokinetic studies have not been performed.

Gender:

Limited data on women concerning pharmacokinetics of tenofovir, shows that gender does not have a significant effect.

In children and adolescents up to 18 years of age:

In children and adolescents (below 18 years of age) pharmacokinetic studies have not been conducted.

In different ethnic groups, pharmacokinetic characteristics have not been specifically studied.

Renal failure

Pharmacokinetic parameters of tenofovir has been determined on 40 patients with various degrees of renal failure, as defined according to baseline creatinine clearance (CrCl), without HIV or hepatitis B infection (CrCl > 80 ml/min, renal functions normal; CrCl = 50-79 ml/min, mild renal failure; CrCl = 30-49 ml/min, moderate renal failure; CrCl = 10-29 ml/min, severe renal failure). Compared to patients with normal renal function, mean (% CV) tenofovir exposure has increased from 2185 (12 %) ng.hour/ml to 30.064 (30 %) ng.hour/ml, 6009 (42 %) ng.hour/ml and 15.985 (45 %) ng.hour/ml, respectively in patients with mild, moderate and severe renal failure. In patients with renal failure, it is expected that increasing dose recommendations will cause higher peak plasma concentrations and lower C_{min} levels compared to patients with normal renal function. Clinical effects of the same are unknown.

In patients with end stage renal diseases, requiring hemodialysis (CrCl < 10 ml/min), tenofovir concentrations, achieved at hour 48 between dialysis, are C_{max} 1,032 ng/ml and mean AUC_{0-48} hours 42,857 ng.hour/ml. It is suggested that the dose range for 245 mg tenofovir disoproxil fumarate must be adjusted for patients with creatinine clearance < 50 ml/min or patients with end stage renal diseases, who require dialysis (see. Section 4.2).

In patients with creatinine clearance < 10 ml/min, who do not receive hemodialysis, who receive peritoneal or other dialysis forms, the pharmacokinetics of tenofovir has not been studied.

Hepatic Failure

Single dose 245 mg tenofovir disoproxil fumarate has been administered to patients, who have varying degrees of hepatic failure, as defined according to Child-Pugh-Turcotte (CPT) classification and who are not infected with HIV, hepatitis B. Pharmacokinetic characteristics of tenofovir has not significantly changed in patients with hepatic failure; this shows that there is no need for dose adjustment in these patients. In patients with normal hepatic function mean (CV %) C_{max} and $AUC_{0-\infty}$ tenofovir are 223 (34.8%) ng/ml and 2,050 (50.8%) ng.hour/ml, respectively; these values are 289 (%46.0) ng/ml and 2,310 (43.5%) ng.hour/ml

and in patients with severe hepatic failure, these values are 305 (24.8%) ng/ml and 2,740 (44.0%) ng.hour/ml.

Intracellular pharmacokinetics

In non-proliferated human mononuclear cells (PBMC), while elimination half-life of tenofovir diphosphate is 50 hours, in PBMCs, stimulated by phytohemagglutinins, elimination half-life has been found as 10 hours.

5.3. Pre-clinical safety data

Pre-clinical studies on rats, dogs and monkeys have shown that there was a decrease in target organ effects in gastrointestinal tract, kidney and bone and a decrease in serum phosphate concentration. Bone toxicity diagnosis has been made as osteomalacia (in monkeys) and decrease in bone mineral density (in rats and dogs). Findings in rat and monkey studies, have shown that there was a substance-related decrease in intestinal absorption of phosphate and a potential secondary decrease in bone mineral density. However, no conclusions could be derived from the mechanisms, underlying these toxicities.

Reproduction studies have been conducted on rats and rabbits. No effects have been determined on mating or fertility parameters or on pregnancy or fetal parameters. There were no significant fetal changes on soft tissue or skeletal tissue. In peri-, post-natal toxicity studies, tenofovir disoproxil fumarate has mitigated the survival index of offsprings and their weight.

In genotoxicity studies tenofovir disoproxil fumarate has been shown to be negative in in vivo mouse bone marrow micronucleus assay, yet as positive for induction of advanced mutations in the presence or absence of S9 metabolic activation, in in vitro L5178Y mouse lymphoma cell assay. tenofovir disoproxil fumarate is positive in Ames test (TA 1535 strain) in two of three studies, one with (increase by 6.2 to 6.8 times) and one without S9 mixture. tenofovir disoproxil fumarate is weakly positive in an unplanned in vivo/in vitro DNA synthesis test, on primary rat hepatocytes.

Tenofovir disoproxil fumarate has not shown any carcinogenic potential in a long-term oral carcinogenicity study on rats. A long-term oral carcinogenicity study, conducted on rats, has shown that at a dose of 600 mg/kg/day, duodenal tumors in gastrointestinal tract, thought to be associated with high local concentrations of tenofovir disoproxil fumarate, had a low incidence. While tumor formation mechanism is uncertain, it is unlikely that these findings will be applicable to humans.

6. PHARMACEUTICAL CHARACTERISTICS

6.1. List of excipients

Pregelatinized Starch

Croscarmellose sodium

Lactose monohydrate

Microcrystalline cellulose

Magnesium stearate

HPMC 2910/Hypromellose

Titanium dioxide

Triacetin

FD&C Blue #2/Indigo Carmine Aluminum Salt

6.2. Incompatibilities

Not applicable.

6.3. Shelf-life

24 months

6.4. Special warnings for storage

Keep at room temperature below 25 °C.

6.5 Nature and content of the package

Contains 30 tablets in white HDPE bottle with silica gel desiccant, in a cardboard box.

6.6. The disposal of remnants of human medicinal product and other special precautions

Unused products or waste materials must be disposed in accordance with “Regulation concerning Control of Medical Wastes” and “Regulation concerning Control of Packages and Package Wastes.”

7. AUTHORIZATION HOLDER

Santa Farma İlaç San. A.Ş.
Okmeydanı, Boruçiçeği Sok. No: 16
34382 Şişli- İSTANBUL
0212 220 64 00
0212 222 57 59

8. AUTHORIZATION NUMBER(S)

2014 /888

9. DATE OF INITIAL GRANT/RENEWAL OF AUTHORIZATION

Initial authorization date: 16.12.2014

Date of authorization renewal: ---

10. DATE OF RENEWAL OF SoPC
