SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

HEPA-TAF 25 mg film coated tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient:

Each film-coated tablet contains 31.09 mg tenofovir alafenamide fumarate equivalent to 25 mg tenofovir alafenamide.

Excipients:

Lactose monohydrate (obtained from cow's milk) 94,96 mg

See 6.1 for a list of excipients.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Yellow, round, film-coated tablets.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

HEPA-TAF is indicated for the treatment of chronic hepatitis B (CHB) in adults and adolescents 12 years of age and older weighing at least 35 kg (see section 5.1).

4.2. Posology and method of administration

Treatment should be initiated by a physician experienced in the treatment of chronic hepatitis B.

Posology/ frequency and duration of administration:

Adults and adolescents aged 12 years and over weighing at least 35 kg: One tablet once a day.

Method of administration:

For oral administration.

HEPA-TAF should be taken with food (See Section 5.2).

Discontinuation of treatment

Discontinuation of treatment may be evaluated as follows (see section 4.4):

- In HBeAg-positive patients without cirrhosis, treatment should be administered at least 6-12 months after HBe seroconversion (HBeAg loss and HBV DNA loss by anti-HBe detection) is confirmed or until HBs seroconversion or loss of efficacy (See Section 4.4). Regular remonitoring is recommended after treatment discontinuation to detect virological relapse.
- In HBeAg-negative patients without cirrhosis, treatment should be administered at least until HBs seroconversion or evidence of loss of efficacy occurs. For treatments extended beyond 2 years, regular reassessment is recommended to confirm that continuing the chosen treatment remains appropriate for the patient.

Missed dose

If a dose is missed and less than 18 hours have passed since the dose would normally be taken, the patient should take HEPA-TAF as soon as possible and then resume the normal dosing schedule. If more than 18 hours have passed since HEPA-TAF is normally taken, the patient should not take the missed dose and simply continue the normal dosing schedule.

If the patient vomits within 1 hour of taking HEPA-TAF, another tablet should be taken. If the patient vomits more than 1 hour after taking HEPA-TAF, he does not need to take another tablet.

Additional information about special populations:

Renal failure:

No dosage adjustment is required for HEPA-TAF in adults or adolescents (at least 12 years of age and weighing at least 35 kg) with an estimated creatinine clearance (CrCl) ≥15 mL/min or in patients undergoing hemodialysis with a CrCl <15 mL/min.

On hemodialysis days, HEPA-TAF should be administered after completion of hemodialysis treatment (See Section 5.2).

There are no dosage recommendations for patients not receiving hemodialysis and with creatinine clearance <15 mL/min (See Section 4.4).

Liver failure

No dosage adjustment of HEPA-TAF is necessary in patients with hepatic impairment (see sections 4.4 and 5.2).

Pediatric population

The safety and effectiveness of HEPA-TAF in children younger than 12 years and body weight <35 kg have not yet been established. There is no data on this subject.

Geriatric population

No dosage adjustment of HEPA-TAF is necessary in patients aged 65 years and over (See Section 5.2).

4.3. Contraindications

It is contraindicated in patients with hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4. Special warnings and precautioons for use

Discontinuation of hepatitis B therapy, including HEPA-TAF, may result in a severe acute hepatitis B exacerbation. Hepatic function, including HEPA-TAF, should be closely monitored with both clinical and laboratory monitoring for at least several months in patients who discontinue hepatitis B therapy. If appropriate, re-initiation of hepatitis B therapy should be considered.

Hepatitis B Virus (HBV) transmission

Patients should be informed that HEPA-TAF does not prevent the risk of transmitting HBV to other people through sexual contact or contamination with blood. Appropriate precautions should continue to be taken.

Patients with decompensated liver disease

There are limited data on the safety and efficacy of HEPA-TAF in HBV-infected patients with decompensated liver disease and a Child Pugh Turcotte (CPT) score > 9 (i.e. class C). These patients may be at higher risk of experiencing hepatic or renal serious adverse reactions. Therefore, hepatobiliary and renal parameters should be closely monitored in this patient population (See Section 5.2).

Worsening of hepatitis

Exacerbations during treatment

Spontaneous worsenings in chronic hepatitis B are quite common and are characterized by transient increases in serum alanine aminotransferase (ALT). Serum ALT may increase in some patients after initiation of antiviral therapy. In patients with compensated liver disease, these

elevations in serum ALT usually occur without being accompanied by an increase in serum bilirubin concentrations or hepatic decompensation. Patients with cirrhosis may be at higher risk for hepatic decompensation following a hepatitis flare and should therefore be closely monitored during treatment.

Exacerbations after stopping treatment

Worsening of acute hepatitis has also been reported in patients who discontinued treatment for chronic hepatitis B, usually associated with increased plasma HBV DNA levels. The majority of cases are self-limiting, but severe flares, including fatal outcomes, can occur after stopping treatment for chronic hepatitis B. Liver function should be monitored by clinical and laboratory monitoring at repeated intervals for at least 6 months after discontinuation of chronic hepatitis B therapy. If appropriate, it may be necessary to restart chronic hepatitis B treatment.

In patients with advanced liver disease or cirrhosis, discontinuation of treatment is not recommended, as worsening of hepatitis after treatment may lead to hepatic decompensation.

Liver flares are serious and sometimes fatal, especially in patients with decompensated liver disease.

Kidney disorder

Patients with creatinine clearance <30 mL/min

Once daily use of HEPA-TAF in patients with CrCl ≥15 mL/min and <30 mL/min, efficacy and safety of switching from another antiviral regimen to tenofovir alafenamide in an open-label clinical study in virologically suppressed chronic HBV-infected patients based on week ninety-six data regarding the effectiveness and reliability of the transition.

CrCl ≥15 mL/dk ve <30 mL/dk olan hastalarda HEPA-TAF'ın günde bir kez kullanımı, virolojik olarak baskılanmış kronik HBV ile enfekte hastalarda bir açık etiketli klinik çalışmada başka bir antiviral rejimden tenofovir alafenamide geçişin etkililiği ve güvenliliği ile ilgili 96. hafta verilerine dayanmaktadır (See Sections 4.8 and 5.1). Kronik hemodiyalize giren CrCl <15 mL/dk olan HBV ile enfekte hastalarda HEPA-TAF'ın etkililiği ve güvenliliğiyle ilgili çok sınırlı veri bulunmaktadır (Bkz. Bölüm 4.8, 5.1 ve 5.2).

CrCl <15 mL/dak olan ve hemodiyaliz almayan hastalarda HEPA-TAF kullanımı önerilmez (Bkz. Bölüm 4.2).

Nephrotoxicity

Postmarketing cases of renal failure, including acute renal failure and proximal renal tubulopathy, have been reported with products containing tenofovir alafenamide. The potential risk of nephrotoxicity from chronic exposure to low levels of tenofovir due to dosing with tenofovir alafenamide cannot be excluded (see section 5.3).

It is recommended that all patients have their renal function evaluated before or at the time of initiation of treatment with HEPA-TAF and monitored as clinically appropriate during treatment. Discontinuation of HEPA-TAF therapy should be considered in patients with clinically significant decline in renal function or evidence of proximal renal tubulopathy.

Patients coinfected with HBV and Hepatitis C or D virus

There are no data regarding the safety and effectiveness of HEPA-TAF in patients coinfected with hepatitis C (HCV) or D (HDV) virus. For the treatment of hepatitis C (HCV), the concomitant use instructions should be followed (See Section 4.5).

HBV and Human Immunodeficiency Virus (HIV) coinfection

HIV antibody testing should be offered to all HBV-infected patients with unknown HIV-1 infection status before initiating treatment with HEPA-TAF. In patients co-infected with HBV and HIV, HEPA-TAF should be administered with other antiretroviral medicinal products to ensure that the patient receives an appropriate regimen for the treatment of HIV (see section 4.5).

Co-administration of other medicinal products

HEPA-TAF should not be administered with medicinal products containing tenofovir alafenamide, tenofovir disoproxil or adefovir dipivoxil.

HEPA-TAF may be potentiated by certain anticonvulsants (e.g., carbamazepine, oxcarbazepine, phenobarbital, and phenytoin), antimycobacterials (e.g., rifampicin, rifabutin, rifapentine), or yellow jaundice, all of which are P-glycoprotein (P-gp) inducers and may decrease tenofovir alafenamide plasma concentrations. It is not recommended to use it together with St. John's wort.

Coadministration of HEPA-TAF with strong P-gp inhibitors (e.g. itraconazole and ketoconazole) may increase tenofovir alafenamide plasma concentrations. Co-administration is not recommended.

Excipients with known effect

HEPA-TAF contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not use this medicine.

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

Interaction studies have been conducted in adults only.

HEPA-TAF should not be administered with medicinal products containing tenofovir disoproxil, tenofovir alafenamide or adefovir dipivoxil.

Medicinal products that may affect tenofovir alafenamide

Tenofovir alafenamide is transported by P-gp and breast cancer resistance protein (BCRP). Medicinal products that induce P-gp activity (e.g. rifampicin, rifabutin, carbamazepine, phenobarbital or St. John's wort) are expected to reduce tenofovir alafenamide plasma concentrations, which may result in a reduced therapeutic effect of HEPA-TAF. It is not recommended to administer such medicinal products together with HEPA-TAF.

Co-administration of tenofovir alafenamide with medicinal products that inhibit P-gp and BCRP may increase the plasma concentration of tenofovir alafenamide. Coadministration of strong P-gp inhibitors with tenofovir alafenamide is not recommended.

Tenofovir alafenamide is an in vitro substrate of OATP1B1 and OATP1B3. The distribution of tenofovir alafenamide in the body may be affected by OATP1B1 and/or OATP1B3 activity.

Effect of tenofovir alafenamide on other medicinal products

Tenofovir alafenamide is not an inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2D6 in vitro. It is not an inhibitor or inducer of CYP3A in vivo.

Tenofovir alafenamide is not an inhibitor of human uridine diphosphate glucuronosyltransferase (UGT) 1A1 in vitro. It is not known whether tenofovir alafenamide is an inhibitor of other UGT enzymes.

Drug interaction information for HEPA-TAF with potential concomitant medicinal products is summarized in Table 1 below (Increase with "↑" and, decrease with "↓", no change with "↔", twice daily with "b.i.d." with, single dose "s.d." once a day with "q.d." It is shown with). The drug interactions described are based on studies conducted with tenofovir alafenamide or are

potential drug interactions that may occur with HEPA-TAF.

Table 1: Interactions between HEPA-TAF and other medicinal products

Medicinal product according to therapeutic fields	**Effects on drug levels[a,b] Mean rate for EAA, C_{max}, C_{min} (90% confidence interval)**	**Recommendations for application with HEPA-TAF**
ANTICONVULSANTS		
Carbamazepine (300 mg orally, b.i.d.) Tenofovir alafenamide[c] (25 mg orally, s.d.)	*Tenofovir alafenamide* ↓**C_{max}** 0,43 (0,36; 0,51) ↓EAA 0,45 (0,4; 0,51) *Tenofovir* ↓**C_{max}** 0,7 (0,65; 0,74) ↔EAA 0,77 (0,74; 0,81)	It is not recommended to be administered together with HEPA-TAF.
Medicinal product according to therapeutic fields	**Effects on drug levels.[a,b] Mean rate for EAA, C_{max}, C_{min} (90% confidence interval)**	**Recommendations for application with HEPA-TAF**
Oxcarbazepine Phenobarbital	Interaction has not been studied. *Expected:*↓Tenofovir alafenamide	It is not recommended to be administered together with HEPA-TAF.
Phenytoin	Interaction has not been studied. *Expected:*↓Tenofovir alafenamide	It is not recommended to be administered together with HEPA-TAF.
Midazolam[d] (2,5 mg orally, s.d.) Tenofovir alafenamide[c] (25 mg orally, q.d.)	*Midazolam* ↔ **C_{max}** 1,02 (0,92; 1,13) ↔ EAA 1,13 (1,04; 1,23)	No dose adjustment is necessary for midazolam (administered orally or intravenously (IV)).
Midazolam[d] (1 mg IV, s.d.) Tenofovir alafenamid[c] (25 mg orally, q.d.)	*Midazolam* ↔ **C_{max}** 0,99 (0,89; 1,11) ↔ EAA 1,08 (1,04; 1,14)	
ANTIDEPRESSANTS		
Sertraline (50 mg orally, s.d.) Tenofovir alafenamid[e] (10 mg orally, q.d.)	*Tenofovir alafenamide* ↔ **C_{max}** 1 (0,86; 1,16) ↔ EAA 0,96 (0,89; 1,03) *Tenofovir* ↔ **C_{max}** 1,1 (1; 1,21) ↔ EAA 1,02 (1; 1,04) ↔ C_{min} 1,01 (0,99; 1,03)	No dose adjustment is necessary for HEPA-TAF or sertraline.
Sertraline (50 mg orally, s.d.) Tenofovir alafenamide[e] (10 mg orally, q.d.)	*Sertralin* ↔ **C_{max}** 1,14 (0,94; 1,38) ↔ EAA 0,93 (0,77; 1,13)	
ANTIFUNGALLER		

Itraconazole Ketoconazole	Interaction has been not studied. *Expected:* ↑ Tenofovir alafenamid	It is not recommended to be administered together with HEPA-TAF.
ANTIMICOBACTERIALS		
Rifampicin Rifapentine	Interaction has been not studied. *Expected:* ↓Tenofovir alafenamide	It is not recommended to be administered together with HEPA-TAF.
Rifabutin	Interaction has been not studied. *Expected:* ↓Tenofovir alafenamide	It is not recommended to be administered together with HEPA-TAF.
HCV ANTIVIRAL AGENTS		
Sofosbuvir (400 mg orally, q.d.)	Interaction has been not studied *Expected:* ↔ Sofosbuvir ↔ GS-331007	No dose adjustment is required for HEPA-TAF or sofosbuvir.
Medicinal product according to therapeutic fields	**Effects on drug levels.[a,b]** **Mean rate for EAA, C_{mxs}, C_{min} (90% confidence interval)**	**Recommendations for application with HEPA-TAF**
Ledipasvir/sofosbuvir (90 mg/400 mg orally, q.d.) Tenofovir alafenamide[f] (25 mg orally, q.d.)	*Ledipasvir* ↔ C_{max} 1,01 (0,97; 1,05) ↔ EAA 1,02 (0,97; 1,06) ↔ C_{min} 1,02 (0,98; 1,07) *Sofosbuvir* ↔ C_{max} 0,96 (0,89; 1,04) ↔ EAA 1,05 (1,01; 1,09) *GS-331007[g]* ↔ C_{max} 1,08 (1,05; 1,11) ↔ EAA 1,08 (1,06; 1,1) ↔ C_{min} 1,1 (1,07; 1,12) *Tenofovir alafenamide* ↔ C_{max} 1,03 (0,94; 1,14) ↔ EAA 1,32 (1,25; 1,4) *Tenofovir* ↑ C_{max} 1,62 (1,56; 1,68) ↑ EAA 1,75 (1,69; 1,81) ↑ C_{min} 1,85 (1,78; 1,92)	No dose adjustment is required for HEPA-TAF or ledipasvir/sofosbuvir.
Sofosbuvir/velpatasvir (400 mg/100 mg orally, q.d.)	Interaction has not been studied. *Expected:* ↔ Sofosbuvir ↔ GS-331007 ↔ Velpatasvir ↑ Tenofovir alafenamide	No dose adjustment is required for HEPA-TAF or sofosbuvir/velpatasvir.

Sofosbuvir/velpatasvir/voksilaprevir (400 mg/100 mg/ 100 mg + 100 mg[i] orally, q.d.) Tenofovir alafenamide[f] (25 mg orally, q.d.)	*Sofosbuvir* ↔ C_{max} 0,95 (0,86; 1,05) ↔ EAA 1,01 (0,97; 1,06) *GS-331007*[g] ↔ C_{max} 1,02 (0,98; 1,06) ↔EAA 1,04 (1,01; 1,06) *Velpatasvir* ↔ C_{max} 1,05 (0,96; 1,16) ↔ EAA 1,01 (0,94; 1,07) ↔C_{min} 1,01 (0,95; 1,09) *Voksilaprevir* ↔ C_{max} 0,96 (0,84; 1,11) ↔ EAA 0,94 (0,84; 1,05) ↔ C_{min} 1,02 (0,92; 1,12) *Tenofovir alafenamid* ↑ C_{max} 1,32 (1,17; 1,48) ↑ EAA 1,52 (1,43; 1,61)	No dose adjustment is required for HEPA-TAF or sofosbuvir/velpatasvir/voxilaprevir.
Medicinal product according to therapeutic fields	**Effects on drug levels.[a,b]** **Mean rate for EAA, C_{mxs}, C_{min} (90% confidence interval)**	**Recommendations for application with HEPA-TAF**
HIV ANTIRETROVIRAL AGENTS – PROTEASE INHIBITORS		
Atazanavir/cobicistat (300 mg/150 mg orally, q.d.) Tenofovir alafenamide[c] (10 mg orally, q.d.)	*Tenofovir alafenamide* ↑ C_{max} 1,8 (1,48; 2,18) ↑ EAA 1,75 (1,55; 1,98) *Tenofovir* ↑ C_{max} 3,16 (3; 3,33) ↑ EAA 3,47 (3,29; 3,67) ↑ C_{min} 3,73 (3,54; 3,93) *Atazanavir* ↔ C_{max} 0,98 (0,94; 1,02) ↔ EAA 1,06 (1,01; 1,11) ↔ C_{min} 1,18 (1,06; 1,31) *Cobicistat* ↔ C_{max} 0,96 (0,92; 1) ↔ EAA 1,05 (1; 1,09) ↑ C_{min} 1,35 (1,21; 1,51)	It is not recommended to be administered together with HEPA-TAF.

Atazanavir/ritonavir (300 mg/100 mg orally, q.d.) Tenofovir alafenamide[c] (10 mg orally, s.d.)	*Tenofovir alafenamide* ↑ C_{max} 1,77 (1,28; 2,44) ↑ EAA 1,91 (1,55; 2,35) *Tenofovir* ↑ C_{max} 2,12 (1,86; 2,43) ↑ EAA 2,62 (2,14; 3,2) *Atazanavir* ↔ C_{max} 0,98 (0,89; 1,07) ↔ EAA 0,99 (0,96; 1,01) ↔ C_{min} 1 (0,96; 1,04)	It is not recommended to be administered together with HEPA-TAF.
Darunavir/cobicistat (800 mg/150 mg orally, q.d.) Tenofovir alafenamide[c] (25 mg orally, q.d.)	*Tenofovir alafenamide* ↔ C_{max} 0,93 (0,72; 1,21) ↔ EAA 0,98 (0,8; 1,19) *Tenofovir* ↑ C_{max} 3,16 (3; 3,33) ↑ EAA 3,24 (3,02; 3,47) ↑ C_{min} 3,21 (2,9; 3,54) *Darunavir* ↔ C_{max} 1,02 (0,96; 1,09) ↔ EAA 0,99 (0,92; 1,07) ↔ C_{min} 0,97 (0,82; 1,15) *Cobicistat* ↔ C_{max} 1,06 (1; 1,12) ↔ EAA 1,09 (1,03; 1,15) ↔ C_{min} 1,11 (0,98; 1,25)	It is not recommended to be administered together with HEPA-TAF.
Medicinal product according to therapeutic fields	**Effects on drug levels[a,b]** **Mean rate for EAA, C_{max}, C_{min} (90% confidence interval)**	**Recommendations for application with HEPA-TAF**
Darunavir/ritonavir (800 mg/100 mg orally, q.d.) Tenofovir alafenamide[c] (10 mg orally, s.d.)	*Tenofovir alafenamide* ↑ C_{max} 1,42 (0,96; 2,09) ↔ EAA 1,06 (0,84; 1,35) *Tenofovir* ↑ C_{max} 2,42 (1,98; 2,95) ↑ EAA 2,05 (1,54; 2,72) *Darunavir* ↔ C_{max} 0,99 (0,91; 1,08) ↔ EAA 1,01 (0,96; 1,06) ↔ C_{min} 1,13 (0,95; 1,34)	It is not recommended to be administered together with HEPA-TAF.

Lopinavir/ritonavir (800 mg/200 mg orally, q.d.) Tenofovir alafenamide[c] (10 mg orally, s.d.)	*Tenofovir alafenamide* ↑ C_{max} 2,19 (1,72; 2,79) ↑ EAA 1,47 (1,17; 1,85) *Tenofovir* ↑ C_{max} 3,75 (3,19; 4,39) ↑ EAA 4,16 (3,5; 4,96) *Lopinavir* ↔ C_{max} 1 (0,95; 1,06) ↔ EAA 1 (0,92; 1,09) ↔ C_{min} 0,98 (0,85; 1,12)	It is not recommended to be administered together with HEPA-TAF.
Tipranavir/ritonavir	Interaction has not been studied. *Expected:* ↓ Tenofovir alafenamide	It is not recommended to be administered together with HEPA-TAF.
HIV ANTIRETROVIRAL AGENTS - INTEGRASE INHIBITORS		
Dolutegravir (50 mg orally, q.d.) Tenofovir alafenamide[c] (10 mg orally, s.d.)	*Tenofovir alafenamide* ↑ C_{max} 1,24 (0,88; 1,74) ↑ EAA 1,19 (0,96; 1,48) *Tenofovir* ↔ C_{max} 1,1 (0,96; 1,25) ↑ EAA 1,25 (1,06; 1,47) *Dolutegravir* ↔ C_{max} 1,15 (1,04; 1,27) ↔ EAA 1,02 (0,97; 1,08) ↔ C_{min} 1,05 (0,97; 1,13)	No dose adjustment is required for HEPA-TAF or dolutegravir.
Raltegravir	Interaction has not been studied. *Expected:* ↔ Tenofovir alafenamide ↔ Raltegravir	No dose adjustment required for HEPA-TAF or raltegravir
Medicinal product according to therapeutic fields	**Effects on drug levels.[a,b]** **Mean rate for EAA, C_{max}, C_{min} (90% confidence interval)**	**Recommendations for application with HEPA-TAF**
HIV ANTIRETROVIRAL AGENTS - NON-NUCLOSIDE REVERSE TRANSCRIPTASE INHIBITORS		
Efavirenz (600 mg orally, q.d.) Tenofovir alafenamide[h] (40 mg orally, q.d.)	*Tenofovir alafenamide* ↓ C_{max} 0,78 (0,58; 1,05) ↔ EAA 0,86 (0,72; 1,02) *Tenofovir* ↓ C_{max} 0,75 (0,67; 0,86) ↔ EAA 0,8 (0,73; 0,87) ↔ C_{min} 0,82 (0,75; 0,89) *Expected:* ↔ Efavirenz	No dose adjustment is required for HEPA-TAF or efavirenz.
Nevirapine	Interaction has been not studied. *Expected:* ↔ Tenofovir alafenamide	No dose adjustment is required for HEPA-TAF or nevirapine.

	↔ Nevirapine	
Rilpivirine (25 mg orally, q.d.) Tenofovir alafenamide (25 mg orally, q.d.)	*Tenofovir alafenamide* ↔ C_{max} 1,01 (0,84; 1,22) ↔ EAA 1,01 (0,94; 1,09) *Tenofovir* ↔ C_{max} 1,13 (1,02; 1,23) ↔ EAA 1,11 (1,07; 1,14) ↔ C_{min} 1,18 (1,13; 1,23) *Rilpivirine* ↔ C_{max} 0,93 (0,87; 0,99) ↔ EAA 1,01 (0,96; 1,06) ↔ C_{min} 1,13 (1,04; 1,23)	No dose adjustment is required for HEPA-TAF or rilpivirine.
HIV ANTIRETROVIRAL AGENTS – CCR5 RECEPTOR ANTAGONIST		
Maraviroc	Interaction has been not studied. *Expected:* ↔ Tenofovir alafenamide ↔ Maraviroc	No dose adjustment is required for HEPA-TAF or maraviroc.
HERBAL SUPPLEMENTS		
St. John's wort (Hypericum perforatum)	Interaction has been not studied. *Expected:* ↓Tenofovir alafenamid	It is not recommended to be administered together with HEPA-TAF.
ORAL CONTRACEPTIVES		
Norgestimate (0,180 mg/0,215 mg/0,250 mg orally, q.d.) Ethinyl estradiol (0,025 mg orally, q.d.) Tenofovir alafenamide[c] (25 mg orally, q.d.)	*Norelgestromin* ↔ *C_{max} 1,17 (1,07; 1,26)* ↔ *EAA 1,12 (1,07; 1,17)* ↔ *C_{min} 1,16 (1,08; 1,24)* *Norgestrel* ↔ *C_{max} 1,1 (1,02; 1,18)* ↔ *EAA 1,09 (1,01; 1,18)* ↔ *C_{min} 1,11 (1,03; 1,2)* *Ethinyl estradiol* ↔ *C_{max} 1,22 (1,15; 1,29)* ↔ *EAA 1,11 (1,07; 1,16)* ↔ *C_{min} 1,02 (0,93; 1,12)*	No dose adjustment is necessary for HEPA-TAF or norgestimate/ethinyl estradiol.

a. All interaction studies were performed on healthy volunteers.

b. All No Effect Limits are 70% - 143%.

c. Study conducted with emtricitabine/tenofovir alafenamide fixed dose combination tablet.

d. A sensitive CYP3A4 substrate.

e. Study conducted with elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide fixed dose combination tablet.

f. Study conducted with emtricitabine/rilpivirine/tenofovir alafenamide fixed dose combination tablet.

g. The predominant circulating nucleoside metabolite of sofosbuvir.

h. Study conducted with tenofovir alafenamide 40 mg and emtricitabine 200 mg.

i. Study conducted with additional voxilaprevir 100 mg to achieve expected voxilaprevir exposures in HCV-infected patients.

Additional information about special population

Pediatric population:

The safety and effectiveness of HEPA-TAF in children younger than 12 years and body weight <35 kg have not yet been established. There is no data on this subject.
Interaction studies have been conducted in adults only.

4.6. Pregnancy and Lactation

General advice

Pregnancy category: B

Women with childbearing potential/Birth control (Contraception)

HEPA-TAF should be administered in conjunction with effective contraception in women of childbearing potential.

Pregnancy period

No or limited data are available from the use of tenofovir alafenamide in pregnant women (fewer than 300 pregnancy outcomes). However, a large body of data in pregnant women (over 1000 exposures) does not indicate malformation or fetal/neonatal toxicity associated with the use of tenofovir disoproxil.

Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy/embryonic/fetal development/birth or postnatal development (see section 5.3).

The use of tenofovir alafenamide during pregnancy may be considered if necessary. Caution should be taken when giving it to pregnant women.

Lactation period

It is not known whether tenofovir alafenamide passes into breast milk. However, studies in animals have shown that tenofovir passes into milk. There is insufficient information regarding the effects of tenofovir on neonates/infants.
The risk to the breastfed newborn/infant cannot be excluded; therefore, tenofovir alafenamide should not be used during breast-feeding.

Reproductive ability/Fertility

There are no human data on the effect of tenofovir alafenamide on fertility. Animal studies do not indicate harmful effects of tenofovir alafenamide on fertility.

4.7. Effects on the ability to drive and use machines

HEPA-TAF may have minor effects on the ability to drive and use machines. Patients should be informed that dizziness has been reported during HEPA-TAF therapy.

4.8. Undesirable effects

Summary of the safety profile

Evaluation of adverse reactions is based on clinical trial data and post-marketing data. In pooled safety data from 2 controlled Phase 3 studies (GS-US-320-0108 and GS-US-320-0110; "Study 108" and "Study 110," respectively), the most frequently reported adverse reactions at week 96 were headache (12%), nausea (6%) and fatigue (6%). After week 96, patients either continued to receive their initial blinded treatment or received open-label tenofovir alafenamide until week 144.

The safety profile of tenofovir alafenamide was similar in virologically suppressed patients switching from tenofovir disoproxil to tenofovir alafenamide in the 108 Study, the 110 Study, and a controlled Phase 3 study GS-US-320-4018 (4018 Study). Changes in lipid laboratory tests were observed following switching from tenofovir disoproxil in these studies (see section 5.1).

Tabulated summary of adverse reactions

The following adverse drug reactions have been identified with tenofovir alafenamide in patients with chronic hepatitis B (See Table 2). Advers reaksiyonlar vücut sistem organ sınıfına ve sıklığına göre 96. hafta verilerine göre aşağıda listelenmektedir. Sıklıklar şu şekilde tanımlanmaktadır: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1.000 to <1/100); rare (≥1/10.000 to <1/1.000); very rare (<1/10.000), not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 2: List of adverse drug reactions detected with Tenofovir alafenamide

System organ class	
Frequency	**Adverse drug reactions**
Nervous system diseases	
Very common:	Headache
Common:	Dizziness
Gastrointestinal diseases	
Common:	Diarrhea, vomiting, nausea, abdominal pain, abdominal bloating, gas
Hepato-biliary diseases	
Common:	High ALT
Skin and subcutaneous tissue diseases	
Common:	Rash, itching
Uncommon:	Angioedema*, urticaria*
Musculoskeletal disorders, connective tissue and bone diseases	
Common:	Arthralgia
General disorders and diseases related to the application area	
Common:	Fatigue

*This adverse reaction has been identified from post-marketing experience for medicinal products containing tenofovir alafenamide.

In an open-label Phase 2 study (GS-US-320-4035; "Study 4035") evaluating the efficacy and safety of switching from another antiviral regimen to tenofovir alafenamide in virologically suppressed chronic HBV-infected patients, from baseline to week 96, small median increases in fasting total cholesterol, direct LDL, HDL, and triglyceride levels were observed in volunteers with moderate or severe renal impairment (Part A Cohort 1) and in volunteers with moderate or severe hepatic impairment (Part B) and this situation is consistent with the changes in Studies 108 and 110. Volunteers with ESRD on hemodialysis in Part A, Cohort 2 had small median decreases in total cholesterol, LDL, and triglyceride levels from baseline to week 96, while small median increases in HDL were observed. The median (Q1, Q3) change from baseline to week 96 in the total cholesterol/HDL ratio was 0,1 (-0,4; 0,4) in the moderate or severe renal impairment group, 0,4 (-0,8-0,1) in volunteers with ESRD on hemodialysis, and 0,1 (-0,2; 0,4) in volunteers with moderate or severe hepatic impairment.

Metabolic parameters

Body weight and blood lipids and glucose levels may increase during treatment.

Other special populations

Until the 96th week in Study 4035, no additional adverse reactions to tenofovir alafenamide were identified in virologically suppressed patients who moderate to severe renal impairment (eGFR 15 to 59 mL/min by Cockcroft-Gault method; Part A, Cohort 1, N=78), end-stage renal disease on hemodialysis (ESRD) (eGFR < 15 mL/min) (Part A, Group 2, N = 15), and/or moderate to severe hepatic impairment (classified as Child-Pugh Class B or C at screening or history; Part B, N=31), switched to tenofovir alafenamide from another antiviral regime.

Reporting of suspected adverse reactions

It is of great importance to report suspected adverse drug reactions after registration. Reporting allows continuous monitoring of the benefit/risk balance of the drug. Healthcare professionals are required to report any suspected adverse reactions to the Turkish Pharmacovigilance Center (TÜFAM). (www.titck.gov.tr; e-posta: tufam@titck.gov.tr; tel: 0 800 314 00 08; faks: 0312 218 35 99).

4.9. Overdose and its treatment

If overdose occurs, the patient should be monitored for evidence of toxicity (See Section 4.8). Treatment of overdose with tenofovir alafenamide consists of general supportive measures, including monitoring of vital signs as well as observation of the patient's clinical condition.

Tenofovir was effectively removed by hemodialysis with an extraction coefficient of approximately 54%. It is not known whether tenofovir can be removed by peritoneal dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamics properties

Pharmacotherapeutic group: Antiinfectives for systemic use, antivirals for systemic use, direct-acting antivirals, nucleoside and nucleotide reverse transcriptase inhibitors
ATC code: J05AF13

Mechanism of action

Tenofovir alafenamide is a phosphonoamidate prodrug (2'-deoxyadenosine monophosphate analogue) of tenofovir. Tenofovir alafenamide enters primary hepatocytes by passive diffusion

and hepatic uptake transporters OATP1B1 and OATP1B3. Tenofovir alafenamide is hydrolyzed primarily by carboxylesterase 1 in primary hepatocytes to form tenofovir. Intracellular tenofovir is then phosphorylated into its pharmacologically active metabolite tenofovir diphosphate. Tenofovir diphosphate inhibits HBV replication by incorporation into viral DNA by HBV reverse transcriptase, resulting in DNA chain termination.

Tenofovir shows specific activity against hepatitis B virus and human immunodeficiency virus (HIV-1 and HIV-2). Tenofovir diphosphate is a weak inhibitor of mammalian DNA polymerases, including mitochondrial DNA polymerase γ, and there is no evidence of in vitro mitochondrial toxicity based on various tests, including mitochondrial DNA assays.

Antiviral activity

The antiviral activity of tenofovir alafenamide was evaluated against a panel of HBV clinical isolates representing genotypes A-H in HepG2 cells. EC50 (50% effective concentration) values for tenofovir alafenamide range from 34,7 to 134,4 nM, with an overall mean EC_{50} of 86,6 nM. In HepG2 cells, the CC_{50} (50% cytotoxic concentration) was >44400 nM.

Resistance

Sequence analysis was performed on matched baseline and on-treatment HBV isolates in patients receiving tenofovir alafenamide, in patients experiencing virologic breakthrough (HBV DNA ≥69 IU/mL at 2 consecutive visits after HBV DNA <69 IU/mL or a 1 log10 or greater increase in HBV DNA from nadir), at week 48 or week 96 or at week 24 or in patients with HBV DNA ≥69 IU/mL at early discontinuation.

In a pooled analysis at week 48 (N=20) and week 96 (N=72) in patients receiving tenofovir alafenamide in Study 108 and Study 110, no amino acid substitution associated with resistance to tenofovir alafenamide was identified in these isolates (genotypic and phenotypic analyses).

In virologically suppressed patients, following switching from tenofovir disoproxil to tenofovir alafenamide, in Study 4018 for 96 weeks, one patient in the TAF-TAF group experienced a virological breakthrough (HBV DNA ≥69 IU/mL at one visit) during treatment and one patient in the TDF-TAF group experienced a virological breakout. No

HBV amino acid substitutions associated with resistance to TAF or TDF were detected during 96 weeks of treatment.

Cross resistance

The antiviral activity of tenofovir alafenamide was evaluated against a panel of isolates containing nucleos(t)ide reverse transcriptase inhibitor mutations in HepG2 cells. HBV isolates expressing the rtV173L, rtL180M, and rtM204V/I substitutions associated with lamivudine resistance remained susceptible to tenofovir alafenamide (<2-fold change in EC_{50} value). HBV isolates expressing rtL180M, rtM204V plus rtT184G, rtS202G, or rtM250V substitutions associated with entecavir resistance remained susceptible to tenofovir alafenamide. HBV isolates associated with adefovir resistance HBV isolates expressing the rtA181T rtA181V, or rtN236T single substitutions remained susceptible to tenofovir alafenamide; however, the HBV isolate expressing rtA181V plus rtN236T exhibited lower susceptibility to tenofovir alafenamide (3,7-fold change in EC_{50} value). The clinical significance of these substitutions is unknown.

Clinical data

The efficacy and safety of tenofovir alafenamide in patients with chronic hepatitis B were based on data from two randomized, double-blind, active-controlled studies, Study 108 and Study 110, at 48 and 96 weeks. The safety of tenofovir alafenamide is also supported by pooled data from patients who continued to receive their blinded treatment from weeks 96 to 144 in Study 108 and Study 110 and from patients in the open-label phase from weeks 96 to 144 in Study 108 and Study 110 (N=360 continued taking tenofovir alafenamide; N=180 switched from tenofovir disoproxil to tenofovir alafenamide at week 96).

In Study 108, HBeAg-negative treatment-naive and treatment-naive patients with compensated liver function were randomized 2:1 to receive tenofovir alafenamide (25 mg; N=285) once daily or tenofovir disoproxil (245 mg; N=140) once daily. Average age was 46 years, 61% male, 72% Asian, 25% White, and 2% (8 volunteers) Black; 24%, 38% and 31% had HBV genotypes B, C and D, respectively. 21% had received prior treatment (prior treatment with antivirals including entecavir (N=41), lamivudine (N=42), tenofovir disoproxil (N=21), or other (N=18) drugs). At baseline, mean plasma HBV DNA was 5.8 log10 IU/mL, mean serum ALT was 94 U/L, and 9% of patients had a history of cirrhosis.

In Study 110, HBeAg-positive treatment-naive and treatment-naive patients with compensated liver function were randomized 2:1 to receive tenofovir alafenamide (25 mg; N=581) once daily or tenofovir disoproxil (245 mg; N=292) once daily. The average age was 38 years, 64% were male, 82% were Asian, 17% were White, and 1% (5 volunteers) were Black. 17%, 52% and 23% have HBV genotypes B, C and D, respectively. 26% had received treatment before (prior treatment with antivirals including adefovir (N=42), entecavir (N=117), lamivudine (N=84), telbivudine (N=25), tenofovir disoproxil (N=70), or other (N=17) drugs). At baseline, mean plasma HBV DNA was 7,6 log10 IU/mL, mean serum ALT was 120 U/L, and 7% of patients had a history of cirrhosis.

In both studies, the primary efficacy endpoint at week 48 was the proportion of patients with plasma HBV DNA levels below 29 IU/mL. Compared to tenofovir disoproxil, HEPA-TAF met noninferiority criteria in obtaining less than 29 IU/mL HBV DNA.
Treatment results for Study 108 and Study 110 up to week 48 are presented in Table 3 and Table 4.

Table 3: HBV DNA efficacy parameters[a] at week 48

	Study 108 **(HBeAg Negative)**		***Study 110*** **(HBeAg Positive)**	
	TAF (N=285)	**TDF (N=140)**	**TAF (N=581)**	**TDF (N=292)**
HBV DNA <29 IU/mL	%94	%93	%64	%67
Treatment difference[b]	%1,8 (%95 CI = -%3,6 to %7,2)		-%3,6 (%95 CI = -%9,8 to %2,6)	
HBV DNA ≥29 IU/mL	%2	%3	%31	%30
Beginning HBV DNA <7 $\log_{10}$ IU/mL ≥7 $\log_{10}$ IU/mL	%96 (221/230) %85 (47/55)	%92 (107/116) %96 (23/24)	N/A	N/A
Beginning HBV DNA <8 $\log_{10}$ IU/mL ≥8 $\log_{10}$ IU/mL	N/A	N/A	%82 (254/309) %43 (117/272)	%82 (123/150) %51 (72/142)
Have not taken nucleosides before[c] Have taken nucleosides before	%94 (212/225) %93 (56/60)	%93 (102/110) %93 (28/30)	%68 (302/444) %50 (69/137)	%70 (156/223) %57 (39/69)
No virological data at week 48	%4	%4	%5	%3
Discontinued study drug due to lack of effectiveness	0	0	< %1	0
Those who discontinued study drug due to AE or death	%1	%1	%1	%1
Those who discontinued study medication for other reasons[d]	%2	%3	%3	%2
Those who received study medication within the window but whose data are missing	< %1	%1	< %1	0

N/A: Not applicable
TAF: Tenofovir alafenamide
TDF: Tenofovir disoproxide
a. Missing: Failed analysis.
b. Adjusted for baseline plasma HBV DNA categories and oral antiviral therapy status strata.
c. Treatment-naïve subjects received <12 weeks of oral antiviral therapy with any nucleoside or nucleotide analogue, including tenofovir disoproxil or tenofovir alafenamide.
d. Adverse Event (AE) includes patients who discontinue treatment for reasons other than death or lack or loss of efficacy (e.g. withdrawal of consent, loss of follow-up, etc.).

Table 4: Additional efficacy parameters[a] at week 48

	Study 108 **(HBeAg Negative)**		***Study 110*** **(HBeAg Positive)**	
	TAF (N=285)	**TDF (N=140)**	**TAF (N=581)**	**TDF (N=292)**
ALT Normalized ALT (Central lab)[b]	%83	%75	%72	%67
Normalized ALT (AASLD)[c]	%50	%32	%45	%36
Serology HBeAg loss/ seroconversion[d]	N/A	N/A	%14 / %10	%12 / %8
HBsAg loss/ seroconversion	0 / 0	0 / 0	%1 / %1	< %1 / 0

N/A: Not applicable
TAF: Tenofovir alafenamide
TDF: Tenofovir disoproxil
a. Missing: Failed analysis.
b. The population used in the analysis of ALT normalization included only patients whose ALT was above the central laboratory's upper limit of normal (ULN) at baseline. The central laboratory ULN for ALT is as follows: ≤43 U/L for men aged 18 to <69 years and ≤35 U/L for men aged ≥69 years; ≤34 U/L for women aged 18 to <69 years and ≤32 U/L for women aged ≥69 years.
c. The population used in the analysis of ALT normalization included only patients whose ALT was above the 2016 American Association for the Study of Liver Diseases (AASLD) criteria ULN of >30 U/L for men and >19 U/L for women at baseline.
d. The population used in the serology analysis included only patients who were antigen (HBeAg positive) and antibody (HBeAb) negative or deficient at baseline.

Experience after 48 weeks in Study 108 and Study 110

At week 96, biochemical and serological responses as well as viral suppression were maintained with uninterrupted tenofovir alafenamide treatment (See Table 5).

Table 5: HBV DNA and additional efficacy parameters[a] at week 96

	Study 108 **(HBeAg Negative)**		***Study 110*** **(HBeAg Positive)**	
	TAF (N=285)	**TDF (N=140)**	**TAF (N=581)**	**TDF (N=292)**
HBV DNA <29 IU/mL	%90	%91	%73	%75
Beginning HBV DNA <7 $\log_{10}$ IU/mL ≥7 $\log_{10}$ IU/mL	%90 (207/230) %91 (50/55)	%91 (105/116) %92 (22/24)	N/A	N/A

Beginning HBV DNA <8 log_{10} IU/mL ≥8 log_{10} IU/mL	N/A	N/A	%84 (260/309) %60 (163/272)	%81 (121/150) %68 (97/142)
Have not taken nucleosides before[b] Have taken nucleosides before	%90 (203/225) %90 (54/60)	%92 (101/110) %87 (26/30)	%75 (331/444) %67 (92/137)	%75 (168/223) %72 (50/69)
ALT Normalized ALT (Central lab)[c] Normalized ALT (AASLD)[d]	%81 %50	%71 %40	%75 %52	%68 %42
Serology **HBeAg loss/ seroconversion**	N/A	N/A	%22 / %18	%18 / %12
HBsAg loss/seroconversion	<%1 / <%1	0 / 0	%1 / %1	%1 / 0

N/A: Not applicable
TAF: Tenofovir alafenamide
TDF: Tenofovir disoproxil
a. Missing: Failed analysis
b. Treatment-naïve subjects received <12 weeks of oral antiviral therapy with any nucleoside or nucleotide analogue, including tenofovir disoproxil or tenofovir alafenamide.
c. The population used in the analysis of ALT normalization included only patients with ALT above the central laboratory upper limit (ULN) at baseline. The central laboratory ULN for ALT is as follows: ≤43 U/L for men aged 18 to <69 years and ≤35 U/L for men aged ≥69 years; ≤34 U/L for women aged 18 to <69 years and ≤32 U/L for women aged ≥69 years.
d. The population used in the analysis of ALT normalization included only patients with ALT above the ULN of the 2016 AASLD criteria at baseline (>30 U/L men and >19 U/L women).
e. The population used in the serology analysis included only patients who were antigen (HBeAg) positive and antibody (HBeAb) negative or missing at baseline.

Changes in bone mineral density measurements in Study 108 and Study 110

In both studies, tenofovir alafenamide was associated with smaller mean reductions in bone mineral density (BMD; measured by hip and lumbar spine dual energy X-ray absorptiometry [DXA] analysis) compared to tenofovir disoproxil after 96 weeks of treatment.

In patients who continued to receive blinded treatment after week 96, the mean percent change in BMD in each group at week 144 was similar to that at week 96. In patients who continued tenofovir alafenamide therapy from week 96 to week 144 in the open-label phase of both studies, the mean percentage change in BMD was +0,4% at the lumbar spine and +0,3% at the total hip, for those switching from tenofovir disoproxil to tenofovir alafenamide at week 96, the increase was +2% in the lumbar spine and +0.9% in the total hip.

Changes in renal function measurements in Study 108 and Study 110

In both studies, tenofovir alafenamide was associated with lower changes in renal safety parameters (Smaller median decreases in Cockcroft-Gault estimated CrCl and smaller median increases in urine protein to creatinine ratio and urine beta-2-microglobulin to creatinine ratio) compared to tenofovir disoproxil after 96 weeks of treatment (See also Section 4.4).

In patients who continued to receive blinded treatment after week 96 in Study 108 and Study 110, the change from baseline in renal laboratory parameter values at week 144 was similar to that at week 96 in each group. In the open-label phase of Study 108 and Study 110, the mean change in serum creatinine (±SD) from week 96 to week 144 was +0,002 (0,0924) mg/dL in those who continued to receive tenofovir alafenamide, the mean change in serum creatinine was -0,018 (0,0691) mg/dL in those switching from tenofovir disoproxil to tenofovir alafenamide at week 96. In the open-label phase, the mean change in eGFR from week 96 to week 144 was -1.2 mL/min in patients continuing to receive tenofovir alafenamide and +4,2 mL/min in patients switching from tenofovir disoproxil to tenofovir alafenamide at week 96.

Changes in lipid laboratory tests in Study 108 and Study 110

In a pooled analysis of Studies 108 and 110, median changes from baseline to week 96 in fasting lipid parameters were observed in both treatment groups. For patients switching to open-label tenofovir alafenamide at week 96, Changes from double-blind baseline in total cholesterol, high-density lipid (HDL) cholesterol, low-density lipid (LDL) cholesterol, triglycerides, and total cholesterol/HDL at week 96 and week 144 for patients initially randomized to tenofovir alafenamide and tenofovir disoproxil is presented in Table 6. At the end of the 96th week, the end of the double-blind phase, decreases in median fasting total cholesterol and HDL and increases in median fasting direct LDL and triglyceride levels were observed in the tenofovir alafenamide group, while the tenofovir disoproxil group exhibited median decreases in all parameters.

In the open-label phase of Studies 108 and 110, patients were switched to open-label tenofovir alafenamide at week 96, while lipid parameters at week 144 were similar to those at week 96 in patients who continued to receive tenofovir alafenamide, median increases in fasting total cholesterol, direct LDL, HDL, and triglycerides were observed in patients switching from tenofovir disoproxil to tenofovir alafenamide at week 96. Median (Q1, Q3) change in total cholesterol/HDL ratio from week 96 to week 144 in the open-label phase was 0 (-0,2; 0,4) in

patients continuing to receive tenofovir alafenamide. It was 0,2 (-0,2; 0,6) in patients switching from tenofovir disoproxil to tenofovir alafenamide at week 96.

Table 6: Median changes from double-blind baseline in lipid laboratory tests at weeks 96 and 144 for patients switching to open-label tenofovir alafenamide at week 96

	TAF-TAF (N=360)		
	Double blind start	**Week 96**	**Week 144**
	Median (Q1, Q3) (mg/dL)	Median change (Q1, Q3) (mg/dL)	Median change (Q1, Q3) (mg/dL)
Total cholesterol (fasting)	185 (166, 210)	0 (-18, 17)	0 (-16, 18)
HDL Cholesterol (fasting)	59 (49, 72)	-5 (-12, 1)[a]	-5 (-12, 2)[b]
LDL Cholesterol (fasting)	113 (95, 137)	6 (-8, 21)[a]	8 (-6, 24)[b]
Triglycerides (fasting)	87 (67, 122)	8 (-12, 28)[a]	11 (-11, 40)[b]
Total Cholesterol/HDL Ratio	3,1 (2,6, 3,9)	0,2 (0 , 0,6)[a]	0,3 (0 , 0,7)[b]
	TDF-TAF (N=180)		
	Double blind start	**Week 96**	**Week 144**
	Median (Q1, Q3) (mg/dL)	Median change (Q1, Q3) (mg/dL)	Median change (Q1, Q3) (mg/dL)
Total cholesterol (fasting)	189 (163, 215)	-23 (-40, -1)[a]	1 (-17, 20)
HDL Cholesterol (fasting)	61 (49, 72)	-12 (-19, -3)[a]	-8 (-15, -1)[b]
LDL Cholesterol (fasting)	120 (95, 140)	-7 (-25, 8)[a]	9 (-5, 26)[b]
Triglycerides (fasting)	89 (69, 114)	-11 (-31, 11)[a]	14 (-10, 43)[b]
Total Cholesterol/HDL Ratio	3,1 (2,5, 3,7)	0,2 (-0,1, 0,7)[a]	0,4 (0 , 1)[b]

TAF: Tenofovir alafenamide
TDF: Tenofovir disoproxil
a. P-value was calculated for change from double-blind baseline at week 96 from the Wilcoxon Signed Rank test and was statistically significant ($p < 0,001$).
b. P-value was calculated for change from double-blind baseline at week 144 from the Wilcoxon Signed Rank test and was statistically significant ($p < 0,001$).

Virologically suppressed adult patients in Study 4018

The efficacy and safety of tenofovir alafenamide in virologically suppressed adults with chronic hepatitis B are based on 48-week data from Study 4018, a randomized, double-blind, active-controlled study (N=243 using tenofovir alafenamide; N=245 using tenofovir disoproxil) and this includes data from patients who participated in the open-label phase of Study 4018 from week 48 to week 96 (remaining on tenofovir alafenamide [TAF-TAF] N=235; [TDF-TAF] N=237 switching from tenofovir disoproxil to tenofovir alafenamide at week 48).

In Study 4018, HBV DNA < lower limit of quantitation (LLOQ) at least 12 weeks before screening and HBV DNA < 20 IU/mL at screening, according to local laboratory assessment, virologically suppressed adults with chronic hepatitis B (N=488) previously maintained on tenofovir disoproxil 245 mg once daily for at least 12 months were enrolled.

Patients were stratified by HBeAg status (HBeAg-positive or HBeAg-negative) and age (≥50 or <50 years) and assigned a 1:1 ratio to switch to 25 mg tenofovir alafenamide (N=243) or continue 245 mg tenofovir disoproxil once daily were randomized (N=245).

The median age was 51 years (22% ≥ 60 years), 71% male, 82% Asian, 14% White, and 68% HBeAg negative. At baseline, the median duration of prior tenofovir disoproxil therapy in the tenofovir alafenamide and tenofovir disoproxil groups was 220 and 224 weeks, respectively. Prior treatment with antivirals also included interferon (N=63), lamivudine (N=191), adefovir dipivoxil (N=185), entecavir (N=99), telbivudine (N=48), or others (N=23). At baseline, median serum ALT was 27 U/L, median eGFR by Cockcroft-Gault was 90,5 mL/min; 16% of patients have a history of cirrhosis.

The primary efficacy endpoint was the proportion of patients with plasma HBV DNA levels ≥20 IU/mL at week 48 (as determined by the modified US FDA Snapshot algorithm). Additional efficacy endpoints included the proportion of patients with HBV DNA levels <20 IU/mL, ALT normal and ALT normalization, HBsAg loss and seroconversion, and HBeAg loss and seroconversion. Tenofovir alafenamide was non-inferior to tenofovir disoproxil in the proportion of subjects with HBV DNA ≥20 IU/mL at week 48 as assessed by the modified US FDA Snapshot algorithm. Treatment outcomes at week 48 (HBV DNA <20 IU/mL using the missing=fail approach) were similar between treatment groups in subgroups separated by age, gender, race, baseline HBeAg status, and ALT.

Treatment results from Study 4018 at week 48 and week 96 are presented in Table 7 and Table 8.

Tablo 7: HBV DNA efficacy parameters at week 48[a,b] and week 96[b,c]

	TAF (N=243)	**TDF (N=245)**	**TAF-TAF (N=243)**	**TDF-TAF (N=245)**
	Week 48		**Week 96**	
HBV DNA ≥20 IU/mL[b,d]	1 (%0,4)	1 (%0,4)	1 (%0,4)	1 (%0,4)
Treatment Difference[e]	%0 (%95 CI = -%1,9 to %2)		%0 (%95 CI = -%1,9 to %1,9)	
HBV DNA <20 IU/mL	234 (%96,3)	236 (%96,3)	230 (%94,7)	230 (%93,9)
Treatment Difference[e]	%0 (95% CI = -%3,7 to %3,7)		%0,9 (95% CI = -%3,5 to %5,2)	
No Virological Data	8 (%3,3)	8 (%3,3)	12 (%4,9)	14 (%5,7)
Those Who	2 (%0,8)	0	3 (%1,2)	1 (%0,4)

Discontinued Study Drug Due to AE or Death and Last Available HBV DNA <20 IU/mL				
Those Who Discontinued Study Drug for Other Reasons and with Last Available HBV DNA <20 IU/mL	6 (%2,5)	8 (%3,3)	7 (%2,9)	11 (%4,5)
Working within the Window Those Who Have Taken the Medicine but Have Missing Data	0	0	2 (%0,8)	2 (%0,8)

TDF : Tenofovir disoproxil
TAF: Tenofovir alafenamide
a. The 48th week window is between day 295 and day 378 inclusive.
b. As determined by the modified US FDA Snapshot algorithm.
c. The open label phase is between days 589 and 840 inclusive of the 96-week window.
d. No patients discontinued treatment due to lack of effectiveness.
e. Adjusted for baseline age groups (<50, ≥50) and baseline HBeAg status strata.
f. AE includes patients who discontinue treatment for reasons other than death or lack of efficacy (e.g. withdrawal of consent, loss of follow-up, etc.).

Table 8: Additional efficacy parameters at week 48 and week 96[a]

	TAF (N=243)	**TDF (N=245)**	**TAF-TAF (N=243)**	**TDF-TAF (N=245)**
	Week 48		**Week 96**	
ALT				
Normal ALT (Central Lab)	%89	%85	%88	%91
Normal ALT (AASLD)	%79	%75	%81	%87
Normalized ALT (Central Lab)[b,c,d]	%50	%37	%56	%79
Normalized ALT (AASLD)[e,f,g]	%50	%26	%56	%74
Serology				
HbeAg Loss / Seroconversion[h]	%8 / %3	%6 / 0	%18 / %5	%9 / %3
Loss of HBsAg / Seroconversion	0 / 0	%2 / 0	%2 / %1	%2 / <%1

TDF : Tenofovir disoproxil
TAF : Tenofovir alafenamide
a. Incomplete: failed analysis
b. The population used in the analysis of ALT normalization included only patients whose ALT was above the upper limit of normal (ULN) of the central laboratory range (>43 U/L men 18 to <69 years and >35 U/L men ≥69 years; >34 U/L women 18 to <69 years and >32 U/L women ≥69 years) at baseline.
c. Percentage of patients at week 48: TAF, 16/32; TDF, 7/19.
d. Percentage of patients at week 96: TAF, 18/32; TDF, 15/19.
e. The population used in the analysis of ALT normalization included only patients with ALT above the ULN of the 2018 American Association for the Study of Liver Diseases (AASLD) criteria at baseline (35 U/L men and 25 U/L women).
f. Percentage of patients at week 48: TAF, 26/52; TDF, 14/53.
g. Percentage of patients at week 48: TAF, 29/52; TDF, 39/53
h. The population used in the serology analysis included only patients who were antigen (HBeAg) positive and antibody (HBeAb) negative or missing at baseline.

Changes in bone mineral density in Study 4018

The mean percent change in BMD from baseline to week 48, as assessed by DXA, was +1,7% with tenofovir disoproxil compared to −1% with tenofovir disoproxil at the lumbar spine and +0,7% compared to −0,5% at the total hip. At week 48, 4% of tenofovir alafenamide patients and 17% of tenofovir disoproxil patients had a BMD decrease of more than 3% at the lumbar spine. At week 48, 2% of tenofovir alafenamide patients and 12% of tenofovir disoproxil patients had a BMD decrease of more than 3% at the total hip.

In the open-label phase, the mean percent change in BMD from baseline to week 96 in patients remaining on tenofovir alafenamide was +2,3% at the lumbar spine and +1,2% at the total hip; it was +1,7% at lumbar spine and +0,2% at total hip in those switching from tenofovir disoproxil to tenofovir alafenamide at week 48.

Changes in renal laboratory tests in Study 4018

By the Cockcroft-Gault method, the mean change in eGFR from baseline to week 48 was +2,2 mL/min in the tenofovir alafenamide group and −1,7 mL/min in those receiving tenofovir disoproxil. At week 48, there was a median increase from baseline in serum creatinine (0,01 mg/dL) in patients randomized to continue treatment with tenofovir disoproxil compared with a median decrease from baseline among those switched to tenofovir alafenamide (-0,01 mg/dL).

In the open-label phase, the median change in eGFR from baseline to week 96 was 1,6 mL/min in patients remaining on tenofovir alafenamide treatment; it was +0,5 mL/min in patients switching from tenofovir disoproxil to tenofovir alafenamide at week 48. The median change in serum creatinine from baseline to week 96 was -0.02 mg/dL in those who remained on tenofovir alafenamide treatment and -0.01 mg/dL in those who switched from tenofovir disoproxil to tenofovir alafenamide at week 48.

Changes in lipid laboratory tests in Study 4018

Changes in total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, and total cholesterol/HDL ratio from double-blind baseline to week 48 and week 96 are presented in Table 9.

Table 9: Median changes in lipid laboratory tests at week 48 and week 96

	TAF (N=236)	**TAF (N=226)**	**TAF-TAF (N=220)**	**TDF (N=230)**	**TDF (N=222)**	**TDF-TAF (N=219)**
	Beginning	**Week 48**	**Week 96**	**Beginning**	**Week 48**	**Week 96**
	(Q1, Q3) (mg/dL)	Median change[a] (Q1, Q3) (mg/dL)	Median change[a] (Q1, Q3) (mg/dL)	(Q1, Q3) (mg/dL)	Median change[a] (Q1, Q3) (mg/dL)	Median change[a] (Q1, Q3) (mg/dL)
Total cholesterol (fasting)	166 (147, 189)	19 (6, 33)	16 (3 , 30)	169 (147, 188)	-4 (-16, 8)	15 (1, 28)
HDL Cholesterol (fasting)	48 (41, 56)	3 (-1, 8)	4 (-1 , 10)	48 (40, 57)	-1 (-5, 2)	4 (0 , 9)
LDL Cholesterol (fasting)	102 (87,123)	16 (5, 27)	17 (6, 28)	103 (87, 120)	1 (-8, 12)	14 (3, 27)
Triglycerides (fasting)[b]	90 (66, 128)	16 (-3, 44)	9 (-8, 28)	89 (68, 126)	-2 (-22, 18)	8 (-8, 38)
Total Kolesterol/ HDL Oranı	3,4 (2,9 , 4,2)	0,2 (-0,1 , 0,5)	0 (-0,3 , 0,3)	3,4 (2,9 , 4,2)	0 (-0,3, 0,3)	0 (-0,3 , 0,3)

TDF: Tenofovir disoproxil
TAF: Tenofovir alafenamide

a. P value was calculated for the difference between TAF and TDF groups at week 48 from the Wilcoxon Rank Sum test and statistically significant changes (p<0,001) from baseline were found for median changes (Q1, Q3) in total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, and total cholesterol/HDL ratio.

b. The number of triglyceride (fasting) patients for the TAF group was N=235 at baseline, N=225 at week 48, and N=218 for the TAF-TAF group at week 96.

Kidney and/or liver impairment in Study 4035

Study 4035 was an open-label clinical trial evaluating the efficacy and safety of switching from another antiviral regimen to tenofovir alafenamide in virologically suppressed chronic HBV-infected patients. Part A of the study included patients with moderate to severe renal impairment (eGFR between 15 and 59 mL/min by Cockcroft-Gault method; Cohort 1, N=78) or patients with ESRD (eGFR <15 mL/min by Cockcroft-Gault method) undergoing hemodialysis (Cohort 2, N=15). Part B of the study included patients (N=31) with moderate to severe hepatic impairment (Child-Pugh Class B or C at screening or history of CPT score ≥7 with any CPT

score ≤12 at screening).

The primary endpoint was the proportion of subjects with HBV DNA <20 IU/mL at week 24. Between secondary efficacy endpoints included at weeks 24 and 96, included were change from baseline in the proportion of subjects achieving HBV DNA <20 IU/mL and detected/not detected (<lowest limit detectable), in the proportion of volunteers with a biochemical response (normal ALT and normalized ALT), in the the proportion of volunteers s with a serological response (loss of HbeAg and seroconversion to anti-Hbe and loss of HbsAg and seroconversion to anti-HBs in HbeAg-positive volunteers) and end-stage liver disease (MELD) scores with CPT in volunteers with liver disease in Part B.

Adult patients with renal impairment in Study 4035, Part A

Initially, HBV DNA <20 IU/mL was detected in 98% (91/93) of the patients in Part A, while HBV DNA value was determined to be undetectable in 66% (61/93). It was noted that the median age was 65 years, 74% of the patients were male, 77% were Asian, 16% were White, and 83% were HBeAg negative. The most commonly used HBV drug oral antivirals were TDF (N = 58), lamivudine (N = 46), adefovir dipivoxil (N = 46) and entecavir (N = 43). At baseline, ALT ≤ULN was detected in 97% and 95% of patients, respectively, according to central laboratory criteria and 2018 AASLD criteria; According to the Cockcroft-Gault method, the median eGFR was determined as 43,7 mL/min (45,7 mL/min in Cohort 1 and 7,32 mL/min in Cohort 2) and it was noted that 34% of the patients had a history of cirrhosis.

Treatment results at weeks 24 and 96 of Study 4035, Part A are presented in Table 10.

Table 10: Efficacy parameters at weeks 24 and 96 for patients with renal impairment

	Cohort 1[a] (N=78)		**Cohort 2[b] (N=15)**		**Total (N=93)**	
	Week 24	Week 96	Week 24	Week 96	Week 24	Week 96 [d]
HBV DNA[c]						
HBV DNA <20 IU/mL	76/78 (%97,4)	65/78 (%83,3)	15/15 (%100)	13/15 (%86,7)	91/93 (%97,8)	78/93 (%83,9)
ALT[c]						
Normal ALT (Central laboratory)	72/78 (%92,3)	64/78 (%82,1)	14/15 (%93,3)	13/15 (%86,7)	86/93 (%92,5)	77/93 (%82,8)
Normal ALT (AASLD)[e]	68/78 (%87,2)	58/78 (%74,4)	14/15 (%93,3)	13/15 (%86,7)	82/93 (%88,2)	71/93 (%76,3)

a. Part A, Cohort 1 includes patients with moderate or severe renal impairment
b. Part A, Cohort 2 includes patients with ESRD undergoing hemodialysis
c. Missing: analysis failure
d. The denominator includes 12 subjects (11 for Cohort 1 and 1 for Cohort 2) who discontinued study medication prematurely
e. 2018 American Association for the Study of Liver Diseases (AASLD) criteria

Adult patients with hepatic impairment in Study 4035, Part B

At baseline, 100% (31/31) of the patients in Part B had HBV DNA <20 IU/mL, while 65% (20/31) had an undetectable HBV DNA level. It was noted that the median age was 57 years (19% in the ≥65 age group), 68% of the patients were male, 81% were Asian, 13% were White, and 90% were HBeAg negative. The most commonly used HBV drug oral antivirals were TDF (N=21), lamivudine (N=14), entecavir (N=14), and adefovir dipivoxil (N = 10). At baseline, ALT ≤ULN was detected in 87% and 68% of patients, respectively, according to central laboratory criteria and 2018 AASLD criteria; according to the Cockcroft-Gault method, median eGFR was determined as 98,5 mL/min; It was noted that 97% of the patients had a history of cirrhosis, with a median (range) CPT score of 6 (5-10) and a median (range) MELD score of 10 (6-17).

Treatment results at weeks 24 and 96 of Study 4035, Part B are presented in Table 11.

Table 11: Efficacy parameters at weeks 24 and 96 for patients with hepatic impairment

	Part B (N=31)	
	Week 24	Week 96[b]
HBV DNA[a]		
HBV DNA <20 IU/mL	31/31 (%100)	24/31 (%77,4)
ALT[a]		
Normal ALT (Central laboratory)	26/31 (%83,9)	22/31 (%71)
Normal ALT (AASLD)[c]	25/31 (%80,6)	18/31 (%58,1)
CPT and MELD Score		
Mean change (SD) from baseline in CPT score	0 (1,1)	0 (1,2)
Mean change (SD) from baseline in MELD score	-0,6 (1,94)	-1 (1,61)

CPT: Child-Pugh Turcotte;
MELD: Latest 24ver liver disease model

a. Incomplete: analysis failure
b. Denominator includes 6 subjects who discontinued study drug prematurely
c. 2018 American Association for the Study of Liver Diseases (AASLD) criteria

Changes in lipid laboratory tests in Study 4035

The small median increases from baseline to weeks 24 and week 96 in total cholesterol, HDL cholesterol, LDL cholesterol, triglyceride level, and total cholesterol/HDL ratio in patients with

renal or hepatic impairment are consistent with findings observed in other studies involving conversion to TAF (See Section 5.1 for 0108, 0110 and 4018 Studies); on the other hand, at the 24th week and the 96th week, decreases compared to baseline in total cholesterol, LDL cholesterol, triglyceride level and total cholesterol/HDL ratio were observed in patients with ESRD undergoing hemodialysis.

Pediatric population:

The European Medicines Agency has deferred the obligation to submit the results of studies with tenofovir alafenamide in one or more subsets of the pediatric population in the treatment of chronic hepatitis B (See Sections 4.2 and 5.2 for information on pediatric use).

5.2. Pharmacokinetic properties

General properties

Absorbation:

Following oral administration of tenofovir alafenamide on an empty stomach in adult patients with chronic hepatitis B, peak plasma concentrations of tenofovir alafenamide were observed at approximately 0,48 hours post-dose. According to the Phase 3 population pharmacokinetic analysis in volunteers with chronic hepatitis B, the mean steady-state AUC_{0-24} values were 0,22 µg•sa/mL and 0,32 µg•sa/m for tenofovir alafenamide (N=698) and tenofovir (N=856), respectively. eady-state C_{max} was 0,18 and 0,02 µg/mL for tenofovir alafenamide and tenofovir, respectively. For fasting conditions, administration of a single dose of tenofovir alafenamide with a high-fat meal resulted in a 65% increase in tenofovir alafenamide exposure.

Distribution:

Tenofovir alafenamide human plasma protein binding was approximately 80% in samples collected during clinical studies. Binding of tenofovir to human plasma proteins is less than 0,7% and is concentration independent in the range of 0,01-25 µg/mL.

Biotransformation:

Metabolism is the major elimination pathway for tenofovir alafenamide in humans, accounting for >80% of the oral dose. In vitro studies have shown that tenofovir alafenamide is metabolized by carboxylesterase-1 in hepatocytes; it is metabolized by cathepsin A in peripheral blood mononuclear cells (PBMC) and macrophages. Tenofovir alafenamide hydrolyzes within cells in vivo to form tenofovir (the major metabolite), which in turn is phosphorylated to the active

metabolite, tenofovir diphosphate.

Tenofovir alafenamide is not metabolized in vitro by CYP1A2, CYP2C8, CYP2C9, CYP2C19, or CYP2D6. Tenofovir alafenamide is minimally metabolized by CYP3A4.

Elimination:

Intact tenofovir alafenamide renal excretion is a minor pathway, with <1% of the dose eliminated in the urine. Tenofovir alafenamide is eliminated primarily after metabolism to tenofovir. The median plasma half-life of tenofovir alafenamide and tenofovir is 0,51 and 32,37 hours, respectively. Tenofovir is renally eliminated from the body by the kidneys by both glomerular filtration and active tubular secretion.

Linearity/non-linearity:

Tenofovir alafenamide exposures are dose proportional over the dose range of 8 to 125 mg.

Pharmacokinetics of special populations

Age, gender and ethnicity:

No clinically significant differences in pharmacokinetics by age or ethnicity were identified. Differences in pharmacokinetics by gender were not found to be clinically significant.

Liver disorder:

Total plasma concentrations of tenofovir alafenamide and tenofovir in patients with severe hepatic impairment are lower than those seen in volunteers with normal liver function. When corrected for protein binding, unbound (free) plasma concentrations of tenofovir alafenamide are similar in severe hepatic impairment and normal liver function.

Kidney disorder:

In studies with tenofovir alafenamide, no clinically significant differences in tenofovir alafenamide or tenofovir pharmacokinetics were observed between healthy volunteers and patients with severe renal impairment (estimated CrCl >15 mL/min but <30 mL/min) (Table 12). Tenofovir exposures in volunteers with ESRD (estimated creatinine clearance <15 mL/min) (N=5) receiving tenofovir alafenamide and undergoing chronic hemodialysis were significantly higher than in volunteers with normal renal function (Table 12). No clinically significant differences in tenofovir alafenamide pharmacokinetics were observed in patients

with ESRD undergoing chronic hemodialysis compared to patients with normal renal function.

Table 12: Pharmacokinetics of tenofovir alafenamide and its metabolite tenofovir in subjects with renal impairment compared to subjects with normal renal function

	AUC (µg.h/mL) Average (%CV)		
Estimated Creatinine Clearance [a]	**Normal kidney function ≥90 mL/min (N=13)b**	**Severe kidney disorder 15–29 mL/min (N=14)b**	**ESRD undergoing hemodialysis <15 mL/min (N=5)c**
Tenofovir alafenamide	0,27 (49,2)[d]	0,51 (47,3)[d]	0,3 (26,7)[e]
Tenofovir	0,34 (27,2)[d]	2,07 (47,1)[d]	18,8 (30,4)[f]

CV: coefficient of variation
a. According to the Cockcroft-Gault method.
b. PK was evaluated in Study GS-US-120-0108 at a single dose of TAF 25 mg in subjects with normal renal function and subjects with severe renal impairment.
c. PK was evaluated before hemodialysis following multiple dose administration of TAF 25 mg in 5 HBV-infected volunteers in Study GS-US-320-4035. In these subjects, median baseline eGFR was 7,2 mL/min (range, 4,8 to 12) by Cockcroft-Gault method.
d. AUC inf.
e. AUC last.
f. AUC tau.

Pediatric population:

The pharmacokinetics of tenofovir alafenamide and tenofovir were evaluated in HIV-1-infected, treatment-naïve adolescents receiving tenofovir alafenamide (10 mg) together with elvitegravir, cobicistat, and emtricitabine as a fixed-dose combination tablet (E/C/F/TAF; Genvoya). No clinically relevant differences in tenofovir alafenamide or tenofovir pharmacokinetics were observed between adolescent and adult HIV-1-infected volunteers.

5.3 Preclinical safety data

Nonclinical studies in rats and dogs have implicated bone and kidneys as the primary target organs of toxicity. Bone toxicity was observed in the form of reduced BMD after tenofovir alafenamide administration in rats and dogs at tenofovir exposures at least four times higher than expected. There was minimal histiocyte infiltration in dog eyes at tenofovir alafenamide and tenofovir exposures approximately 4-fold and 17-fold higher, respectively, than expected after tenofovir alafenamide administration.

Tenofovir alafenamide was not found to be mutagenic or clastogenic in conventional genotoxic assays.

Because there was less tenofovir exposure following tenofovir alafenamide administration in mice and rats compared to tenofovir disoproxil administration, carcinogenicity studies and a perinatal-postnatal study in rats were conducted using tenofovir disoproxil alone. Conventional studies with tenofovir disoproxil (as fumarate) on carcinogenic potential and tenofovir disoproxil (as fumarate) on reproductive and developmental toxicity or tenofovir alafenamide did not reveal any special hazard for humans. Reproductive toxicity studies in rats and rabbits revealed no effects on mating, fertility, pregnancy or fetal parameters. However, in a perinatal-postnatal toxicity study, tenofovir disoproxil at maternally toxic doses reduced the viability index and body weight of the offspring. A long-term oral carcinogenicity study in mice showed a low incidence of duodenal tumors at the high dose of 600 mg/kg/day, which may be related to high local concentrations in the gastrointestinal tract. The mechanism of tumor formation in mice and its potential significance in humans is unknown.

6. PHARMACEUTICAL PROPERTIES

6.1. List of excipients

Tablet core:

Lactose monohydrate (obtained from cow's milk)
Microcrystalline cellulose
Croscarmellose sodium
Colloidal anhydrous silica
Magnesium stearate

Coating Material:

Polyvinyl alcohol (E1203)
Polyethylene glycol / Macrogol (E1521)
Talc (E553b)
Titanium dioxide (E171)
Yellow iron oxide (E172)
Red iron oxide (E172)

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

24 months

6.4. Special precautions for storage

Store at room temperature below 25°C and in its original packaging to protect from moisture. Keep the bottle tightly closed.

6.5. Nature and content of packaging

HEPA-TAF tablets are packaged in high-density polyethylene (HDPE) bottles and lined with an induction-activated aluminum foil liner, closed with a matching fluted, child-safe cap made of polypropylene. Each bottle contains 1 piece of 1 g silica gel desiccant and polyester cotton. A bottle containing 30 film-coated tablets is presented in a cardboard box with instructions for use.

6.6. Disposal of residues of the medicinal product for human use and other special measures

Unused products or waste materials must be disposed of in accordance with the "Medical Waste Control Regulation" and "Packaging Waste Control Regulation".

7. MARKETING AUTHORIZATION HOLDER

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Oğuzlar Mah. 1370. Sok. 7/3 06520 Çankaya-ANKARA
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8. REGISTRATION NUMBER(S)

2023/451

9. FIRST REGISTRATION DATE/ REGISTRATION RENEWAL DATE

First registration date: 15.11.2023
Registration renewal date:

10. RENEWAL DATE OF SPC

15.11.2023