

## SUMMARY OF PRODUCT CHARACTERISTICS

### 1. Name of the medicinal product

**HepBest** (Tenofovir Alafenamide 25 mg) Tablets

### 2. Qualitative and quantitative composition

Each tablet contains:

Tenofovir Alafenamide Fumarate equivalent to Tenofovir Alafenamide 25 mg

Excipient with known effect

Each tablet contains 67.957 mg lactose (as monohydrate).

For the full list of excipients, see section 6.1.

### 3. Pharmaceutical form

Film-coated tablet.

A white to off-white, film-coated, round, biconvex tablet debossed with **M** on one side of the tablet and **TFI** on the other side.

### 4. Clinical particulars

#### 4.1 Therapeutic indications

Tenofovir Alafenamide tablets 25 mg is indicated for the treatment of chronic hepatitis B in adults and adolescents (aged 12 years and older with body weight at least 35 kg) (see section 5.1).

#### 4.2 Posology and method of administration

Therapy should be initiated by a physician experienced in the management of chronic hepatitis B.

Posology

Adults and adolescents (aged 12 years and older with body weight at least 35 kg): one tablet once daily.

*Treatment discontinuation:*

Treatment discontinuation may be considered as follows (see section 4.4):

- In HBeAg positive patients without cirrhosis, treatment should be administered for at least 6-12 months after HBe seroconversion (HBeAg loss and HBV DNA loss with antiHBe detection) is confirmed or until HBs seroconversion or until there is loss of efficacy (see section 4.4). Regular reassessment 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 until there is evidence of loss of efficacy. With prolonged treatment for more than 2 years, regular reassessment is recommended to confirm that continuing the selected therapy remains appropriate for the patient.

*Missed dose:* If a dose is missed and less than 18 hours have passed from the time it is usually taken, the patient should take Tenofovir Alafenamide tablets 25 mg as soon as possible and then resume their normal dosing schedule. If more than 18 hours have passed from the time it is

usually taken, the patient should not take the missed dose and should simply resume the normal dosing schedule.

If the patient vomits within 1 hour of taking Tenofovir Alafenamide tablets 25 mg, the patient should take another tablet. If the patient vomits more than 1 hour after taking Tenofovir Alafenamide tablets 25 mg, the patient does not need to take another tablet.

#### Special populations

##### *Elderly*

No dose adjustment of Tenofovir Alafenamide tablets 25 mg is required in patients aged 65 years and older (see section 5.2).

##### *Renal impairment*

No dose adjustment of Tenofovir Alafenamide tablets 25 mg is required in adults or adolescents (aged at least 12 years and of at least 35 kg body weight) with estimated creatinine clearance (CrCl)  $\geq$  15 mL/min or in patients with CrCl  $<$  15 mL/min who are receiving haemodialysis.

On days of haemodialysis, Tenofovir Alafenamide tablets 25 mg should be administered after completion of haemodialysis treatment (see section 5.2).

No dosing recommendations can be given for patients with CrCl  $<$  15 mL/min who are not receiving haemodialysis (see section 4.4).

##### *Hepatic impairment*

No dose adjustment of Tenofovir Alafenamide tablets 25 mg is required in patients with hepatic impairment (see sections 4.4 and 5.2).

##### *Paediatric population*

The safety and efficacy of Tenofovir Alafenamide tablets 25 mg in children younger than 12 years of age, or weighing  $<$  35 kg, have not yet been established. No data are available.

#### Method of administration

Oral administration. Tenofovir Alafenamide tablets 25 mg should be taken with food.

### **4.3 Contraindications**

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

### **4.4 Special warnings and precautions for use**

#### HBV transmission

Patients must be advised that Tenofovir Alafenamide tablets 25 mg does not prevent the risk of transmission of HBV to others through sexual contact or contamination with blood. Appropriate precautions must continue to be used.

#### Patients with decompensated liver disease

There are no data on the safety and efficacy of Tenofovir Alafenamide tablets 25 mg in HBV infected patients with decompensated liver disease and who have a Child Pugh Turcotte (CPT) score  $>$  9 (i.e. class C). These patients may be at higher risk of experiencing serious hepatic or renal adverse reactions. Therefore, hepatobiliary and renal parameters should be closely monitored in this patient population (see section 5.2).

#### Exacerbation of hepatitis

##### *Flares on treatment*

Spontaneous exacerbations in chronic hepatitis B are relatively common and are characterised by transient increases in serum alanine aminotransferase (ALT). After initiating antiviral therapy, serum ALT may increase in some patients. In patients with compensated liver disease, these

increases in serum ALT are generally not accompanied by an increase in serum bilirubin concentrations or hepatic decompensation. Patients with cirrhosis may be at a higher risk for hepatic decompensation following hepatitis exacerbation, and therefore should be monitored closely during therapy.

#### *Flares after treatment discontinuation*

Acute exacerbation of hepatitis has been reported in patients who have discontinued treatment for hepatitis B, usually in association with rising HBV DNA levels in plasma. The majority of cases are self-limited but severe exacerbations, including fatal outcomes, may occur after discontinuation of treatment for hepatitis B. Hepatic function should be monitored at repeated intervals with both clinical and laboratory followup for at least 6 months after discontinuation of treatment for hepatitis B. If appropriate, resumption of hepatitis B therapy may be warranted.

In patients with advanced liver disease or cirrhosis, treatment discontinuation is not recommended

since post treatment exacerbation of hepatitis may lead to hepatic decompensation. Liver flares are especially serious, and sometimes fatal in patients with decompensated liver disease.

#### Renal impairment

##### *Patients with creatinine clearance < 30 mL/min*

The use of Tenofovir Alafenamide tablets 25 mg once daily in patients with CrCl  $\geq$  15 mL/min but < 30 mL/min and in patients with CrCl < 15 mL/min who are receiving haemodialysis is based on very limited pharmacokinetic data and on modelling and simulation. There are no safety data on the use of Tenofovir Alafenamide tablets 25 mg to treat HBV infected patients with CrCl < 30 mL/min.

The use of Tenofovir Alafenamide tablets 25 mg is not recommended in patients with CrCl < 15 mL/min who are not receiving haemodialysis (see section 4.2).

#### Nephrotoxicity

A potential risk of nephrotoxicity resulting from chronic exposure to low levels of tenofovir due to dosing with tenofovir alafenamide cannot be excluded (see section 5.3).

#### Patients coinfecting with HBV and hepatitis C or D virus

There are no data on the safety and efficacy of Tenofovir Alafenamide tablets 25 mg in patients coinfecting with hepatitis C or D virus. Coadministration guidance for the treatment of hepatitis C should be followed (see section 4.5).

#### Hepatitis B and HIV coinfection

HIV antibody testing should be offered to all HBV infected patients whose HIV1 infection status is

unknown before initiating therapy with Tenofovir Alafenamide tablets 25 mg. In patients who are coinfecting with HBV and HIV, Tenofovir Alafenamide tablets 25 mg should be co administered with other antiretroviral agents to ensure that the patient receives an appropriate regimen for treatment of HIV (see section 4.5).

#### Coadministration with other medicinal products

Tenofovir Alafenamide tablets 25 mg should not be coadministered with products containing tenofovir alafenamide, tenofovir disoproxil fumarate or adefovir dipivoxil.

Coadministration of Tenofovir Alafenamide tablets 25 mg with certain anticonvulsants (e.g. carbamazepine, oxcarbazepine, phenobarbital and phenytoin), antimycobacterials (e.g. rifampicin, rifabutin and rifapentine) or St. John's wort, all of which are inducers of P-glycoprotein (Pgp) and may decrease tenofovir alafenamide plasma concentrations, is not recommended.

Coadministration of Tenofovir Alafenamide tablets 25 mg with strong inhibitors of Pgp (e.g. itraconazole and ketoconazole) may increase tenofovir alafenamide plasma concentrations. Coadministration is not recommended.

#### Lactose intolerance

Tenofovir Alafenamide tablets 25 mg contains lactose monohydrate. Consequently, patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucosegalactose malabsorption should not take this medicinal product.

### 4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

Tenofovir Alafenamide tablets 25 mg should not be coadministered with medicinal products containing tenofovir disoproxil fumarate, tenofovir alafenamide or adefovir dipivoxil.

#### Medicinal products that may affect tenofovir alafenamide

Tenofovir alafenamide is transported by Pgp and breast cancer resistance protein (BCRP). Medicinal products that are Pgp inducers (e.g., rifampicin, rifabutin, carbamazepine, phenobarbital or St. John's wort) are expected to decrease plasma concentrations of tenofovir alafenamide, which may lead to loss of therapeutic effect of Tenofovir Alafenamide tablets 25 mg. Coadministration of such medicinal products with Tenofovir Alafenamide tablets 25 mg is not recommended.

Coadministration of Tenofovir Alafenamide tablets 25 mg with medicinal products that inhibit Pgp

and/or BCRP may increase plasma concentration of tenofovir alafenamide. Coadministration of strong inhibitors of Pgp with Tenofovir Alafenamide tablets 25 mg is not recommended.

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

#### 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 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 Tenofovir Alafenamide tablets 25 mg with potential concomitant medicinal products is summarized in Table 1 below (increase is indicated as “↑”, decrease as “↓”, no change as “↔”; twice daily as “b.i.d.”, single dose as “s.d.”, once daily as “q.d.”; and intravenously as “IV”). The drug interactions described are based on studies conducted with tenofovir alafenamide, or are potential drug interactions that may occur with Tenofovir Alafenamide tablets 25 mg.

**Table 1: Interactions between Tenofovir Alafenamide tablets 25 mg and other medicinal products**

<b>Medicinal product by therapeutic areas</b>	<b>Effects on drug levels.<sup>a,b</sup></b> <b>Mean ratio (90% confidence interval) for AUC, C<sub>max</sub>, C<sub>min</sub></b>	<b>Recommendation concerning co-administration with Tenofovir Alafenamide</b>
<b>ANTICONVULSANTS</b>		

Carbamazepine (300 mg orally, b.i.d.) Tenofovir alafenamide <sup>c</sup> (25 mg orally, s.d.)	<i>Tenofovir alafenamide</i> ↓ C <sub>max</sub> 0.43 (0.36, 0.51) ↓ AUC 0.45 (0.40, 0.51) <i>Tenofovir</i> ↓ C <sub>max</sub> 0.70 (0.65, 0.74) ↔ AUC 0.77 (0.74, 0.81)	Co-administration is not recommended.
Oxcarbazepine Phenobarbital	Interaction not studied. <i>Expected:</i> ↓ Tenofovir alafenamide	Co-administration is not recommended.
Phenytoin	Interaction not studied. <i>Expected:</i> ↓ Tenofovir alafenamide	Co-administration is not recommended.
Midazolam <sup>d</sup> (2.5 mg orally, s.d.) Tenofovir alafenamide <sup>c</sup> (25 mg orally, q.d.)	<i>Midazolam</i> ↔ C <sub>max</sub> 1.02 (0.92, 1.13) ↔ AUC 1.13 (1.04, 1.23)	No dose adjustment of midazolam (administered orally or IV) is required.
Midazolam <sup>d</sup> (1 mg IV, s.d.) Tenofovir alafenamide <sup>c</sup> (25 mg orally, q.d.)	<i>Midazolam</i> ↔ C <sub>max</sub> 0.99 (0.89, 1.11) ↔ AUC 1.08 (1.04, 1.14)	
<b>ANTIDEPRESSANTS</b>		
Sertraline (50 mg orally, s.d.) Tenofovir alafenamide <sup>e</sup> (10 mg orally, q.d.)	<i>Tenofovir alafenamide</i> ↔ C <sub>max</sub> 1.00 (0.86, 1.16) ↔ AUC 0.96 (0.89, 1.03) <i>Tenofovir</i> ↔ C <sub>max</sub> 1.10 (1.00, 1.21) ↔ AUC 1.02 (1.00, 1.04) ↔ C <sub>min</sub> 1.01 (0.99, 1.03)	No dose adjustment of Vemlidy or sertraline is required.
Sertraline (50 mg orally, s.d.) Tenofovir alafenamide <sup>e</sup> (10 mg orally, q.d.)	<i>Sertraline</i> ↔ C <sub>max</sub> 1.14 (0.94, 1.38) ↔ AUC 0.93 (0.77, 1.13)	
<b>ANTIFUNGALS</b>		
Itraconazole Ketoconazole	Interaction not studied. <i>Expected:</i> ↑ Tenofovir alafenamide	Co-administration is not recommended.

<b>ANTIMYCOBACTERIALS</b>		
Rifampicin Rifapentine	Interaction not studied. <i>Expected:</i> ↓ Tenofovir alafenamide	Co-administration is not recommended.
Rifabutin	Interaction not studied. <i>Expected:</i> ↓ Tenofovir alafenamide	Co-administration is not recommended.
<b>HCV ANTIVIRAL AGENTS</b>		
Sofosbuvir (400 mg orally, q.d.)	Interaction not studied. <i>Expected:</i> ↔ Sofosbuvir ↔ GS-331007	No dose adjustment of Vemlidy or sofosbuvir is required.
Ledipasvir/sofosbuvir (90 mg/400 mg orally, q.d.) Tenofovir alafenamide <sup>f</sup> (25 mg orally, q.d.)	<i>Ledipasvir</i> ↔ C <sub>max</sub> 1.01 (0.97, 1.05) ↔ AUC 1.02 (0.97, 1.06) ↔ C <sub>min</sub> 1.02 (0.98, 1.07) <i>Sofosbuvir</i> ↔ C <sub>max</sub> 0.96 (0.89, 1.04) ↔ AUC 1.05 (1.01, 1.09) <i>GS-331007<sup>g</sup></i> ↔ C <sub>max</sub> 1.08 (1.05, 1.11) ↔ AUC 1.08 (1.06, 1.10) ↔ C <sub>min</sub> 1.10 (1.07, 1.12) <i>Tenofovir alafenamide</i> ↔ C <sub>max</sub> 1.03 (0.94, 1.14) ↔ AUC 1.32 (1.25, 1.40) <i>Tenofovir</i> ↑ C <sub>max</sub> 1.62 (1.56, 1.68) ↑ AUC 1.75 (1.69, 1.81) ↑ C <sub>min</sub> 1.85 (1.78, 1.92)	No dose adjustment of Vemlidy or ledipasvir/sofosbuvir is required.
Sofosbuvir/velpatasvir (400 mg/100 mg orally, q.d.)	Interaction not studied. <i>Expected:</i> ↔ Sofosbuvir ↔ GS-331007 ↔ Velpatasvir ↑ Tenofovir alafenamide	No dose adjustment of Vemlidy or sofosbuvir/velpatasvir is required.

<p>Sofosbuvir/velpatasvir/ voxilaprevir (400 mg/100 mg/ 100 mg + 100 mg<sup>i</sup> orally, q.d.)</p> <p>Tenofovir alafenamide<sup>f</sup> (25 mg orally, q.d.)</p>	<p><i>Sofosbuvir</i> ↔ C<sub>max</sub> 0.95 (0.86, 1.05) ↔ AUC 1.01 (0.97, 1.06)</p> <p><i>GS-331007<sup>g</sup></i> ↔ C<sub>max</sub> 1.02 (0.98, 1.06) ↔ AUC 1.04 (1.01, 1.06)</p> <p><i>Velpatasvir</i> ↔ C<sub>max</sub> 1.05 (0.96, 1.16) ↔ AUC 1.01 (0.94, 1.07) ↔ C<sub>min</sub> 1.01 (0.95, 1.09)</p> <p><i>Voxilaprevir</i> ↔ C<sub>max</sub> 0.96 (0.84, 1.11) ↔ AUC 0.94 (0.84, 1.05) ↔ C<sub>min</sub> 1.02 (0.92, 1.12)</p> <p><i>Tenofovir alafenamide</i> ↑ C<sub>max</sub> 1.32 (1.17, 1.48) ↑ AUC 1.52 (1.43, 1.61)</p>	<p>No dose adjustment of Vemlidy or sofosbuvir/velpatasvir/voxilaprevir is required.</p>
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**HIV ANTIRETROVIRAL AGENTS – PROTEASE INHIBITORS**

<p>Atazanavir/cobicistat (300 mg/150 mg orally, q.d.)</p> <p>Tenofovir alafenamide<sup>c</sup> (10 mg orally, q.d.)</p>	<p><i>Tenofovir alafenamide</i> ↑ C<sub>max</sub> 1.80 (1.48, 2.18) ↑ AUC 1.75 (1.55, 1.98)</p> <p><i>Tenofovir</i> ↑ C<sub>max</sub> 3.16 (3.00, 3.33) ↑ AUC 3.47 (3.29, 3.67) ↑ C<sub>min</sub> 3.73 (3.54, 3.93)</p> <p><i>Atazanavir</i> ↔ C<sub>max</sub> 0.98 (0.94, 1.02) ↔ AUC 1.06 (1.01, 1.11) ↔ C<sub>min</sub> 1.18 (1.06, 1.31)</p> <p><i>Cobicistat</i> ↔ C<sub>max</sub> 0.96 (0.92, 1.00) ↔ AUC 1.05 (1.00, 1.09) ↑ C<sub>min</sub> 1.35 (1.21, 1.51)</p>	<p>Co-administration is not recommended.</p>
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<p>Atazanavir/ritonavir (300 mg/100 mg orally, q.d.) Tenofovir alafenamide<sup>c</sup> (10 mg orally, s.d.)</p>	<p><i>Tenofovir alafenamide</i> ↑ C<sub>max</sub> 1.77 (1.28, 2.44) ↑ AUC 1.91 (1.55, 2.35) <i>Tenofovir</i> ↑ C<sub>max</sub> 2.12 (1.86, 2.43) ↑ AUC 2.62 (2.14, 3.20) <i>Atazanavir</i> ↔ C<sub>max</sub> 0.98 (0.89, 1.07) ↔ AUC 0.99 (0.96, 1.01) ↔ C<sub>min</sub> 1.00 (0.96, 1.04)</p>	<p>Co-administration is not recommended.</p>
<p>Darunavir/cobicistat (800 mg/150 mg orally, q.d.) Tenofovir alafenamide<sup>c</sup> (25 mg orally, q.d.)</p>	<p><i>Tenofovir alafenamide</i> ↔ C<sub>max</sub> 0.93 (0.72, 1.21) ↔ AUC 0.98 (0.80, 1.19) <i>Tenofovir</i> ↑ C<sub>max</sub> 3.16 (3.00, 3.33) ↑ AUC 3.24 (3.02, 3.47) ↑ C<sub>min</sub> 3.21 (2.90, 3.54) <i>Darunavir</i> ↔ C<sub>max</sub> 1.02 (0.96, 1.09) ↔ AUC 0.99 (0.92, 1.07) ↔ C<sub>min</sub> 0.97 (0.82, 1.15) <i>Cobicistat</i> ↔ C<sub>max</sub> 1.06 (1.00, 1.12) ↔ AUC 1.09 (1.03, 1.15) ↔ C<sub>min</sub> 1.11 (0.98, 1.25)</p>	<p>Co-administration is not recommended.</p>
<p>Darunavir/ritonavir (800 mg/100 mg orally, q.d.) Tenofovir alafenamide<sup>c</sup> (10 mg orally, s.d.)</p>	<p><i>Tenofovir alafenamide</i> ↑ C<sub>max</sub> 1.42 (0.96, 2.09) ↔ AUC 1.06 (0.84, 1.35) <i>Tenofovir</i> ↑ C<sub>max</sub> 2.42 (1.98, 2.95) ↑ AUC 2.05 (1.54, 2.72) <i>Darunavir</i> ↔ C<sub>max</sub> 0.99 (0.91, 1.08) ↔ AUC 1.01 (0.96, 1.06) ↔ C<sub>min</sub> 1.13 (0.95, 1.34)</p>	<p>Co-administration is not recommended.</p>



Lopinavir/ritonavir (800 mg/200 mg orally, q.d.) Tenofovir alafenamide <sup>c</sup> (10 mg orally, s.d.)	<i>Tenofovir alafenamide</i> ↑ C <sub>max</sub> 2.19 (1.72, 2.79) ↑ AUC 1.47 (1.17, 1.85) <i>Tenofovir</i> ↑ C <sub>max</sub> 3.75 (3.19, 4.39) ↑ AUC 4.16 (3.50, 4.96) <i>Lopinavir</i> ↔ C <sub>max</sub> 1.00 (0.95, 1.06) ↔ AUC 1.00 (0.92, 1.09) ↔ C <sub>min</sub> 0.98 (0.85, 1.12)	Co-administration is not recommended.
Tipranavir/ritonavir	Interaction not studied. <i>Expected:</i> ↓ Tenofovir alafenamide	Co-administration is not recommended.
<b>HIV ANTIRETROVIRAL AGENTS – INTEGRASE INHIBITORS</b>		
Dolutegravir (50 mg orally, q.d.) Tenofovir alafenamide <sup>c</sup> (10 mg orally, s.d.)	<i>Tenofovir alafenamide</i> ↑ C <sub>max</sub> 1.24 (0.88, 1.74) ↑ AUC 1.19 (0.96, 1.48) <i>Tenofovir</i> ↔ C <sub>max</sub> 1.10 (0.96, 1.25) ↑ AUC 1.25 (1.06, 1.47) <i>Dolutegravir</i> ↔ C <sub>max</sub> 1.15 (1.04, 1.27) ↔ AUC 1.02 (0.97, 1.08) ↔ C <sub>min</sub> 1.05 (0.97, 1.13)	No dose adjustment of Vemlidy or dolutegravir is required.
Raltegravir	Interaction not studied. <i>Expected:</i> ↔ Tenofovir alafenamide ↔ Raltegravir	No dose adjustment of Vemlidy or raltegravir is required.
<b>HIV ANTIRETROVIRAL AGENTS – NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS</b>		

<p>Efavirenz (600 mg orally, q.d.) Tenofovir alafenamide<sup>h</sup> (40 mg orally, q.d.)</p>	<p><i>Tenofovir alafenamide</i> ↓ C<sub>max</sub> 0.78 (0.58, 1.05) ↔ AUC 0.86 (0.72, 1.02) <i>Tenofovir</i> ↓ C<sub>max</sub> 0.75 (0.67, 0.86) ↔ AUC 0.80 (0.73, 0.87) ↔ C<sub>min</sub> 0.82 (0.75, 0.89) <i>Expected:</i> ↔ Efavirenz</p>	<p>No dose adjustment of Vemlidy or efavirenz is required.</p>
<p>Nevirapine</p>	<p>Interaction not studied. <i>Expected:</i> ↔ Tenofovir alafenamide ↔ Nevirapine</p>	<p>No dose adjustment of Vemlidy or nevirapine is required.</p>
<p>Rilpivirine (25 mg orally, q.d.) Tenofovir alafenamide (25 mg orally, q.d.)</p>	<p><i>Tenofovir alafenamide</i> ↔ C<sub>max</sub> 1.01 (0.84, 1.22) ↔ AUC 1.01 (0.94, 1.09) <i>Tenofovir</i> ↔ C<sub>max</sub> 1.13 (1.02, 1.23) ↔ AUC 1.11 (1.07, 1.14) ↔ C<sub>min</sub> 1.18 (1.13, 1.23) <i>Rilpivirine</i> ↔ C<sub>max</sub> 0.93 (0.87, 0.99) ↔ AUC 1.01 (0.96, 1.06) ↔ C<sub>min</sub> 1.13 (1.04, 1.23)</p>	<p>No dose adjustment of Vemlidy or rilpivirine is required.</p>
<p><b>HIV ANTIRETROVIRAL AGENTS – CCR5 RECEPTOR ANTAGONIST</b></p>		
<p>Maraviroc</p>	<p>Interaction not studied. <i>Expected:</i> ↔ Tenofovir alafenamide ↔ Maraviroc</p>	<p>No dose adjustment of Vemlidy or maraviroc is required.</p>
<p><b>HERBAL SUPPLEMENTS</b></p>		
<p>St. John's wort (<i>Hypericum perforatum</i>)</p>	<p>Interaction not studied. <i>Expected:</i> ↓ Tenofovir alafenamide</p>	<p>Co-administration is not recommended.</p>
<p><b>ORAL CONTRACEPTIVES</b></p>		

<p>Norgestimate (0.180 mg/0.215 mg/ 0.250 mg orally, q.d.)</p> <p>Ethinylestradiol (0.025 mg orally, q.d.)</p> <p>Tenofovir alafenamide<sup>c</sup> (25 mg orally, q.d.)</p>	<p><i>Norelgestromin</i> ↔ C<sub>max</sub> 1.17 (1.07, 1.26) ↔ AUC 1.12 (1.07, 1.17) ↔ C<sub>min</sub> 1.16 (1.08, 1.24)</p> <p><i>Norgestrel</i> ↔ C<sub>max</sub> 1.10 (1.02, 1.18) ↔ AUC 1.09 (1.01, 1.18) ↔ C<sub>min</sub> 1.11 (1.03, 1.20)</p> <p><i>Ethinylestradiol</i> ↔ C<sub>max</sub> 1.22 (1.15, 1.29) ↔ AUC 1.11 (1.07, 1.16) ↔ C<sub>min</sub> 1.02 (0.93, 1.12)</p>	<p>No dose adjustment of Vemlidy or norgestimate/ethinyl estradiol is required.</p>
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- a All-interaction studies are conducted in healthy volunteers.
- b. All No Effect Boundaries 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

#### 4.6 Fertility, pregnancy and lactation

##### Pregnancy

There are no or limited amount of data (less than 300 pregnancy outcomes) from the use of tenofovir alafenamide in pregnant women. However, a large amount of data on pregnant women (more than 1000 exposed outcomes) indicates no malformative nor feto/neonatal toxicity associated with the use of tenofovir disoproxil fumarate.

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity

(see section 5.3).

The use of Tenofovir Alafenamide tablets 25 mg may be considered during pregnancy, if necessary.

##### Breastfeeding

It is not known whether tenofovir alafenamide is secreted in human milk. However, in animal studies it has been shown that tenofovir is secreted into milk. There is insufficient information on the effects of tenofovir in newborns/infants.

A risk to the breastfed child cannot be excluded; therefore, Tenofovir Alafenamide tablets 25 mg should not be used during breastfeeding.

##### Fertility

No human data on the effect of Tenofovir Alafenamide tablets 25 mg on fertility are available. Animal studies do not indicate harmful effects of tenofovir alafenamide on fertility.

#### 4.7 Effects on ability to drive and use machines

Tenofovir Alafenamide tablets 25 mg has no or negligible influence on the ability to drive and use machines. Patients should be informed that dizziness has been reported during treatment with Tenofovir Alafenamide tablets 25 mg.

#### 4.8 Undesirable effects

Summary of the safety profile

Assessment of adverse reactions is based on safety data from the analysis performed through to the Week 72 analysis (median duration of exposure of 88 weeks), from 2 Phase 3 studies in which 866 HBV infected patients received tenofovir alafenamide 25 mg once daily. The most frequently reported adverse reactions were headache (11%), nausea (6%), and fatigue (6%).

Tabulated summary of adverse reactions

The following adverse drug reactions have been identified with tenofovir alafenamide in patients with chronic hepatitis B (Table 2). The adverse reactions are listed below by body system organ class and frequency. Frequencies are defined as follows: very common ( $\geq 1/10$ ), common ( $\geq 1/100$  to  $< 1/10$ ), uncommon ( $\geq 1/1,000$  to  $< 1/100$ ), rare ( $\geq 1/10,000$  to  $< 1/1,000$ ) or very rare ( $< 1/10,000$ ).

**Table 2: Adverse drug reactions identified with tenofovir alafenamide**

<b>System organ class</b>	
<b>Frequency</b>	<b>Adverse reaction</b>
<i>Nervous system disorders</i>	
Very common	Headache
Common	Dizziness
<i>Gastrointestinal disorders</i>	
Common	Diarrhoea, vomiting, nausea, abdominal pain, abdominal distension, flatulence
<i>Hepatobiliary disorders</i>	
Common	Increased ALT
<i>Skin and subcutaneous tissue disorders</i>	
Common	Rash, pruritus
Uncommon	Angioedema <sup>1</sup> , urticaria <sup>1</sup>
<i>Musculoskeletal and connective tissue disorders</i>	
Common	Arthralgia
<i>General disorders and administration site conditions</i>	
Common	Fatigue

<sup>1</sup> Adverse reaction identified through post-marketing surveillance for tenofovir alafenamide-containing products.

#### Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the TMDA ADR reporting tool; website: <https://imis.tmda.go.tz/arrt> or search for TMDA Adverse Reactions Reporting Tool in the Google Play Store”;

### 4.9 Overdose

If overdose occurs the patient must be monitored for evidence of toxicity (see section 4.8).

Treatment of overdose with Tenofovir Alafenamide tablets 25 mg consists of general supportive measures including monitoring of vital signs as well as observation of the clinical status of the patient.

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

## 5. Pharmacological properties

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiviral for systemic use, nucleoside and nucleotide reverse transcriptase inhibitors; ATC code: J05AF13.

#### Mechanism of action

Tenofovir alafenamide is a phosphoramidate prodrug of tenofovir (2'deoxyadenosine monophosphate analogue). Tenofovir alafenamide enters primary hepatocytes by passive diffusion and by the hepatic

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

Tenofovir has activity that is specific to hepatitis B virus and human immunodeficiency virus (HIV1 and HIV2). Tenofovir diphosphate is a weak inhibitor of mammalian DNA polymerases that include mitochondrial DNA polymerase  $\gamma$  and there is no evidence of mitochondrial toxicity *in vitro* based on several assays including mitochondrial DNA analyses.

#### Antiviral activity

The antiviral activity of tenofovir alafenamide was assessed in HepG2 cells against a panel of HBV clinical isolates representing genotypes AH. The EC<sub>50</sub> (50% effective concentration) values for tenofovir alafenamide ranged from 34.7 to 134.4 nM, with an overall mean EC<sub>50</sub> of 86.6 nM. The CC<sub>50</sub> (50% cytotoxicity concentration) in HepG2 cells was > 44400 nM.

#### Resistance

In a pooled analysis of patients receiving Tenofovir Alafenamide tablets 25 mg, sequence analysis was performed on paired baseline and on treatment HBV isolates for patients who either experienced virologic breakthrough (2 consecutive visits with HBV DNA  $\geq$  69 IU/mL after having been < 69 IU/mL, or 1.0 log<sub>10</sub> or greater increase in HBV DNA from nadir) through Week 48, or had HBV DNA  $\geq$  69 IU/mL at early discontinuation at or after Week 24. No amino acid substitutions associated with resistance to Tenofovir Alafenamide tablets 25 mg were identified in 20 paired isolates.

#### 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 resistance to lamivudine remained susceptible to tenofovir alafenamide (< 2fold change in EC50). HBV isolates expressing the rtL180M, rtM204V plus rtT184G, rtS202G, or rtM250V substitutions associated with resistance to entecavir remained susceptible to tenofovir alafenamide. HBV isolates expressing the rtA181T, rtA181V, or rtN236T single substitutions associated with resistance to adefovir remained susceptible to tenofovir alafenamide; however, the HBV isolate expressing rtA181V plus rtN236T exhibited reduced susceptibility to tenofovir alafenamide (3.7 fold change in EC50). The clinical relevance of these substitutions is not known.

**Clinical data**

The efficacy and safety of Tenofovir Alafenamide tablets 25 mg in patients with chronic hepatitis B are based on 48 week data from two randomized, double blind, active controlled studies, GSUS3200108 (“Study 108”) and GSUS3200110 (“Study 110”).

In Study 108, HBeAg negative treatment naïve and treatment experienced patients with compensated liver function were randomized in a 2:1 ratio to receive Tenofovir Alafenamide tablets 25 mg (25 mg; N = 285) once daily or tenofovir disoproxil fumarate (300 mg; N = 140) once daily. The mean age was 46 years, 61% were male, 72% were Asian, 25% were White and 2% (8 subjects) were Black; 24%, 38%, and 31% had HBV genotype B, C, and D, respectively. 21% were treatment experienced (previous treatment with oral antivirals, including entecavir (N = 41), lamivudine (N = 42), tenofovir disoproxil fumarate (N = 21), or other (N = 18)). 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 naïve and treatment experienced patients with compensated liver function were randomized in a 2:1 ratio to receive Tenofovir Alafenamide tablets 25 mg (25 mg; N = 581) once daily or tenofovir disoproxil fumarate (300 mg; N = 292) once daily. The mean age was 38 years, 64% were male, 82% were Asian, 17% were White and < 1% (5 subjects) were Black. 17%, 52%, and 23% had HBV genotype B, C, and D, respectively. 26% were treatment experienced (previous treatment with oral antivirals, including adefovir (N = 42), entecavir (N = 117), lamivudine (N = 84), telbivudine (N = 25), tenofovir disoproxil fumarate (N = 70), or other (n = 17)). 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.

The primary efficacy endpoint in both trials was the proportion of patients with plasma HBV DNA levels below 29 IU/mL. Tenofovir Alafenamide tablets 25 mg met the noninferiority criteria in achieving HBV DNA less than 29 IU/mL when compared to tenofovir disoproxil fumarate.

Treatment outcomes of Study 108 and Study 110 through Week 48 are presented in Table 3 and Table 4.

Additional outcomes through Week 72 are presented in Table 5.

**Table 3: HBV DNA efficacy parameters at Week 48<sup>a</sup>**

	<b>Study 108 (HBeAg-Negative)</b>		<b>Study 110 (HBeAg-Positive)</b>	
	<b>TAF (N = 285)</b>	<b>TDF (N = 140)</b>	<b>TAF (N = 581)</b>	<b>TDF (N = 292)</b>
<b>HBV DNA &lt; 29 IU/mL</b>	94%	93%	64%	67%
Treatment difference <sup>b</sup>	1.8% (95% CI = -3.6% to 7.2%)		-3.6% (95% CI = -9.8% to 2.6%)	

<b>HBV DNA <math>\geq</math> 29 IU/mL</b>	2%	3%	31%	30%
<b>Baseline HBV DNA</b>				
< 7 log <sub>10</sub> IU/mL	96% (221/230)	92% (107/116)	N/A	N/A
$\geq$ 7 log <sub>10</sub> IU/mL	85% (47/55)	96% (23/24)		
<b>Baseline HBV DNA</b>				
< 8 log <sub>10</sub> IU/mL	N/A	N/A	82% (254/309)	82% (123/150)
$\geq$ 8 log <sub>10</sub> IU/mL			43% (117/272)	51% (72/142)
Nucleoside naïve <sup>c</sup>	94% (212/225)	93% (102/110)	68% (302/444)	70% (156/223)
Nucleoside experienced	93% (56/60)	93% (28/30)	50% (69/137)	57% (39/69)
<b>No Virologic data at Week 48</b>	4%	4%	5%	3%
Discontinued study drug due to lack of efficacy	0	0	< 1%	0
Discontinued study drug due to AE or death	1%	1%	1%	1%
Discontinued study drug due to other reasons <sup>d</sup>	2%	3%	3%	2%
Missing data during window but on study drug	< 1%	1%	< 1%	0

N/A = not applicable

TDF = tenofovir disoproxil fumarate

TAF = tenofovir alafenamide

a. Missing = failure analysis.

b. Adjusted by baseline plasma HBV DNA categories and oral antiviral treatment status strata.

c. Treatment naïve subjects received < 12 weeks of oral antiviral treatment with any nucleoside or nucleotide analog including tenofovir disoproxil fumarate or tenofovir alafenamide.

d. Includes patients who discontinued for reason other than an AE, death or lack or loss of efficacy, e.g. withdrew consent, loss to followup, etc.

**Table 4: Additional efficacy parameters at Week 48<sup>a</sup>**

	<b>Study 108 (HBeAg-Negative)</b>		<b>Study 110 (HBeAg-Positive)</b>	
	<b>TAF (N = 285)</b>	<b>TDF (N = 140)</b>	<b>TAF (N = 581)</b>	<b>TDF (N = 292)</b>
ALT Normalised ALT (Central	83%	75%	72%	67%

Normalised ALT (AASLD) <sup>c</sup>	50%	32%	45%	36%
Serology HBeAg loss /	N/A	N/A	14% / 10%	12% / 8%
HBsAg loss / seroconversion	0 / 0	0 / 0	1% / 1%	< 1% / 0

N/A = not applicable

TDF = tenofovir disoproxil fumarate

TAF = tenofovir alafenamide

a. Missing = failure analysis.

b. The population used for analysis of ALT normalization included only patients with ALT above upper limit of normal (ULN) of the central laboratory range at baseline. Central laboratory ULN for ALT are as follows: ≤ 43 U/L for males aged 18 to < 69 years and ≤ 35 U/L for males ≥ 69 years; ≤ 34 U/L for females 18 to < 69 years and ≤ 32 U/L for females ≥ 69 years.

c. The population used for analysis of ALT normalization included only patients with ALT above ULN of the American Association of the Study of Liver Diseases (AASLD) criteria at baseline. AASLD ULN for ALT criteria are as follows: ≤ 30 U/L for males and ≤ 19 U/L for females.

d. The population used for serology analysis included only patients with antigen positive and antibody negative or missing at baseline

#### *Experience beyond 48 weeks in Study 108 and Study 110*

At Week 96, viral suppression as well as biochemical and serological responses were maintained with continued tenofovir alafenamide treatment (see Table 5).

**Table 5: HBV DNA and additional efficacy parameters at Week 96<sup>a</sup>**

	<b>Study 108 (HBeAg-Negative)</b>		<b>Study 110 (HBeAg-Positive)</b>	
	<b>TAF</b> (N = 285)	<b>TDF</b> (N = 140)	<b>TAF</b> (N = 581)	<b>TDF</b> (N = 292)
<b>HBV DNA &lt; 29 IU/mL</b>	90%	91%	73%	75%
<b>Baseline HBV DNA</b>				
< 7 log <sub>10</sub> IU/mL	90% (207/230)	91% (105/116)	N/A	N/A
≥ 7 log <sub>10</sub> IU/mL	91% (50/55)	92% (22/24)		
<b>Baseline HBV DNA</b>				
< 8 log <sub>10</sub> IU/mL				81% (121/150)
≥ 8 log <sub>10</sub> IU/mL	N/A	N/A	84% (260/309) 60% (163/272)	68% (97/142)



Nucleoside-naïve <sup>b</sup>	90% (203/225)	92% (101/110)	75% (331/444)	75% (168/223)
Nucleoside-experienced	90% (54/60)	87% (26/30)	67% (92/137)	72% (50/69)
<b>ALT</b>				
Normalised ALT (Central lab) <sup>c</sup>	81%	71%	75%	68%
Normalised ALT (AASLD) <sup>d</sup>	50%	40%	52%	42%
<b>Serology</b>				
HBeAg loss / seroconversion <sup>e</sup>	N/A	N/A	22% / 18%	18% / 12%
HBsAg loss / seroconversion	< 1% / < 1%	0 / 0	1% / 1%	1% / 0

N/A = not applicable

TDF = tenofovir disoproxil fumarate

TAF = tenofovir alafenamide

a. Missing = failure analysis

b. Treatment naïve subjects received < 12 weeks of oral antiviral treatment with any nucleoside or nucleotide analogue including tenofovir disoproxil fumarate or tenofovir alafenamide.

c. The population used for analysis of ALT normalization included only patients with ALT above upper

limit of normal (ULN) of the central laboratory range at baseline. Central laboratory ULN for ALT are as follows: ≤ 43 U/L for males aged 18 to < 69 years and ≤ 35 U/L for males ≥ 69 years; ≤ 34 U/L for females 18 to < 69 years and ≤ 32 U/L for females ≥ 69 years.

d. The population used for analysis of ALT normalization included only patients with ALT above ULN of the American Association of the Study of Liver Diseases (AASLD) criteria (> 30 U/L males and > 19 U/L females) at baseline.

#### *Changes in measures of bone mineral density*

In both studies tenofovir alafenamide was associated with smaller percentage decreases in bone

mineral density (BMD; as measured by hip and lumbar spine dual energy X ray absorptiometry [DXA] analysis) compared to tenofovir disoproxil fumarate after 72 weeks of treatment.

#### *Changes in measures of renal function*

In both studies tenofovir alafenamide was associated with smaller changes in renal safety parameters (smaller reductions in estimated CrCl by CockcroftGault and smaller percentage increases in urine protein to creatinine ratio and urine albumin to creatinine ratio) compared to tenofovir disoproxil fumarate after 72 weeks of treatment (see also section 4.4).

#### *Paediatric population*

The European Medicines Agency has deferred the obligation to submit the results of studies with

Tenofovir Alafenamide tablets 25 mg in one or more subsets of the paediatric population in the treatment of chronic hepatitis B (see sections 4.2 and 5.2 for information on paediatric use).

## **5.2 Pharmacokinetic properties**

Absorption

Following oral administration of Tenofovir Alafenamide tablets 25 mg under fasted conditions in adult patients with chronic hepatitis B, peak plasma concentrations of tenofovir alafenamide were observed approximately 0.48 hours postdose. Based on Phase 3 population pharmacokinetic analysis in subjects with CHB, mean steady state AUC<sub>0-24</sub> for tenofovir alafenamide (N = 698) and tenofovir (N = 856) were 0.22 µg•hr/mL and 0.32 µg•hr/mL, respectively. Steady state C<sub>max</sub> for tenofovir alafenamide and tenofovir were 0.18 and 0.02 µg•hr/mL, respectively. Relative to fasting conditions, the administration of a single dose of Tenofovir Alafenamide tablets 25 mg with a high fat meal resulted in a 65% increase in tenofovir alafenamide exposure.

#### Distribution

The binding of tenofovir alafenamide to human plasma proteins in samples collected during clinical trials was approximately 80%. The binding of tenofovir to human plasma proteins is less than 0.7% and is independent of concentration over the range of 0.01–25 µg/mL.

#### Biotransformation

Metabolism is a major elimination pathway for tenofovir alafenamide in humans, accounting for > 80% of an oral dose. *In vitro* studies have shown that tenofovir alafenamide is metabolized to tenofovir (major metabolite) by carboxylesterase1 in hepatocytes; and by cathepsin A in PBMCs and macrophages. *In vivo*, tenofovir alafenamide is hydrolysed within cells to form tenofovir (major metabolite), which is phosphorylated to the active metabolite, tenofovir diphosphate. *In vitro*, tenofovir alafenamide is not metabolized by CYP1A2, CYP2C8, CYP2C9, CYP2C19, or CYP2D6. Tenofovir alafenamide is minimally metabolized by CYP3A4.

#### Elimination

Renal excretion of intact tenofovir alafenamide is a minor pathway with < 1% of the dose eliminated in urine. Tenofovir alafenamide is mainly eliminated following metabolism to tenofovir. Tenofovir alafenamide and tenofovir have a median plasma half life of 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/nonlinearity

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

#### Pharmacokinetics in special populations

##### *Age, gender and ethnicity*

No clinically relevant differences in pharmacokinetics according to age or ethnicity have been identified. Differences in pharmacokinetics according to gender were not considered to be clinically relevant.

##### *Hepatic impairment*

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

##### *Renal impairment*

No clinically relevant differences in tenofovir alafenamide or tenofovir pharmacokinetics were observed between healthy subjects and patients with severe renal impairment (estimated CrCl > 15 but < 30 mL/min) in studies of tenofovir alafenamide.

### *Paediatric population*

The pharmacokinetics of tenofovir alafenamide and tenofovir were evaluated in HIV1infected, treatment naïve adolescents who received tenofovir alafenamide (10 mg) given 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 HIV1infected subjects.

### **5.3 Preclinical safety data**

Nonclinical studies in rats and dogs revealed bone and kidney as the primary target organs of toxicity. Bone toxicity was observed as reduced BMD in rats and dogs at tenofovir exposures at least four times greater than those expected after administration of tenofovir alafenamide. A minimal infiltration of histiocytes was present in the eye in dogs at tenofovir alafenamide and tenofovir exposures of approximately 4 and 17 times greater, respectively, than those expected after administration of tenofovir alafenamide. Tenofovir alafenamide was not mutagenic or clastogenic in conventional genotoxic assays. Because there is a lower tenofovir exposure in rats and mice after tenofovir alafenamide administration compared to tenofovir disoproxil fumarate, carcinogenicity studies and a rat peripostnatal study were conducted only with tenofovir disoproxil fumarate. No special hazard for humans was revealed in conventional studies of carcinogenic potential with tenofovir disoproxil (as fumarate) and reproduction and development with tenofovir disoproxil (as fumarate) or tenofovir alafenamide. Reproductive toxicity studies in rats and rabbits showed no effects on mating, fertility, pregnancy or foetal parameters. However, tenofovir disoproxil fumarate reduced the viability index and weight of pups in a peripostnatal toxicity study at maternally toxic doses. A longterm oral

carcinogenicity study in mice showed a low incidence of duodenal tumours, considered likely related to high local concentrations in the gastrointestinal tract at the high dose of 600 mg/kg/day. The mechanism of tumour formation in mice and potential relevance for humans is uncertain.

## **6. Pharmaceutical particulars**

### **6.1 List of Excipients**

#### ***Core tablet***

Lactose Monohydrate, Microcrystalline Cellulose, Croscarmellose Sodium, Magnesium Stearate

#### ***Film coat***

Polyvinyl Alcohol, Polyethylene Glycol, Titanium Dioxide & Talc.

### **6.2 Incompatibilities**

Not applicable.

### **6.3 Shelf life**

24 months

### **6.4 Special precautions for storage**

Do not store above 30°C. Store in original container.

### **6.5 Nature and contents of container**

HDPE bottle of 30's, 90's & 180's\*

\* Not all packs may be marketed.

### **6.6 Special precautions for disposal**

No special requirements.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

**7. MARKETING AUTHORIZATION HOLDER**

Mylan Laboratories Limited, India  
Plot No.564/A/22, Road No.92, Jubilee Hills  
Hyderabad - 500096,  
Telangana, India.

Tel: 040-39258106

Telefax:040-39258105

E-mail: [kulbhushan.Ganotra@mylan.in](mailto:kulbhushan.Ganotra@mylan.in)

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**10. DATE OF REVISION OF THE TEXT**