**For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory**

**Tenohope E** (Emtricitabine 200mg and Tenofovir Disoproxil Fumarate 300mg Tablets)

**COMPOSITION**
Each film coated tablet contains:
Emtricitabine……..200mg
Tenofovir disoproxil fumarate.....300mg
equivalent to Tenofovir Disoproxil…...245mg

**PRODUCT DESCRIPTION**
Blue colored, Capsule shaped, biconvex, film coated tablets, debossed with 'L 24' on one side of the tablet and plain on other side.

**PHARMACOLOGICAL ACTION**
**Pharmacokinetics**
Absorption

Following oral administration of Tenohope E Tablet, emtricitabine and tenofovir disoproxil are rapidly absorbed and tenofovir disoproxil is converted to tenofovir. Maximum emtricitabine and tenofovir concentrations are observed in serum within 0.5 to 3.0 h of dosing in the fasted state. Administration of Tenohope E with food resulted in a delay of approximately three quarters of an hour in reaching maximum tenofovir concentrations and increases in tenofovir AUC and $C_{max}$ of approximately 35% and 15%, respectively, when administered with a high fat or light meal, compared to administration in the fasted state. In order to optimise the absorption of tenofovir, it is recommended that Tenohope E should preferably be taken with food.

Distribution

Following intravenous administration, the volume of distribution of emtricitabine and tenofovir was approximately 1.4 L/kg and 800 mL/kg, respectively. After oral administration of emtricitabine or tenofovir disoproxil, emtricitabine and tenofovir are widely distributed throughout the body. *In vitro* binding of emtricitabine to human plasma proteins was < 4% and independent of concentration over the range of 0.02 to 200 µg/mL. *In vitro* protein binding of tenofovir to plasma or serum protein was less than 0.7 and 7.2%, respectively, over the tenofovir concentration range 0.01 to 25 µg/mL.

Biotransformation

There is limited metabolism of emtricitabine. The biotransformation of emtricitabine includes oxidation of the thiol moiety to form the 3'-sulphoxide diastereomers (approximately 9% of dose) and conjugation with glucuronic acid to form 2'-O-glucuronide (approximately 4% of dose). It was determined via *in vitro* that neither tenofovir disoproxil nor tenofovir are substrates for the CYP450 enzymes. Neither emtricitabine nor tenofovir inhibited *in vitro* drug metabolism mediated by any of the major human CYP450 isoforms involved in drug biotransformation. Also, emtricitabine did not inhibit uridine-5'-diphosphoglucuronyl transferase, the enzyme responsible for glucuronidation.

Elimination

Emtricitabine is primarily excreted by the kidneys with complete recovery of the dose achieved in urine (approximately 86%) and faeces (approximately 14%). Thirteen percent of the emtricitabine dose was recovered in urine as three metabolites. The systemic clearance of emtricitabine averaged 307 mL/min. Following oral administration, the elimination half-life of emtricitabine is approximately 10 hours.

Tenofovir is primarily excreted by the kidney by both filtration and an active tubular transport system with approximately 70-80% of the dose excreted unchanged in urine following intravenous administration. The apparent clearance of tenofovir averaged approximately 307 mL/min. Renal clearance has been estimated to be approximately 210 mL/min, which is in excess of the glomerular filtration rate. This indicates that active tubular secretion is an important part of the elimination of tenofovir. Following oral administration, the elimination half-life of tenofovir is approximately 12 to 18 hours.

Elderly

Pharmacokinetic studies have not been performed with emtricitabine or tenofovir (administered as tenofovir disoproxil) in the elderly (over 65 years of age).

Gender

Emtricitabine and tenofovir pharmacokinetics are similar in male and female patients.

Ethnicity

No clinically important pharmacokinetic difference due to ethnicity has been identified for emtricitabine. The pharmacokinetics of tenofovir (administered as tenofovir disoproxil) have not been specifically studied in different ethnic groups.

Paediatric population

Pharmacokinetic studies have not been performed with Tenohope E in children and adolescents (under 18 years of age). In general, the pharmacokinetics of emtricitabine in infants, children and adolescents (aged 4 months up to 18 years) are similar to those seen in adults.

The pharmacokinetics of emtricitabine and tenofovir (administered as tenofovir disoproxil) are expected to be similar in HIV-1 infected and uninfected adolescents based on the similar exposures of emtricitabine and tenofovir in HIV-1 infected adolescents and adults, and the similar exposures of emtricitabine and tenofovir in HIV-1 infected and uninfected adults.

Renal impairment

The pharmacokinetics of emtricitabine and tenofovir (administered as tenofovir disoproxil) in paediatric patients with renal impairment have not been studied. No data are available to make dose recommendations

Hepatic impairment

The pharmacokinetics of Tenohope E have not been studied in subjects with hepatic impairment.

**PHARMACODYNAMICS:**

Pharmacotherapeutic group: Antiviral for systemic use; antivirals for treatment of HIV infections, combinations.

ATC code: J05AR03

Mechanism of action

Emtricitabine is a nucleoside analogue of cytidine. Tenofovir disoproxil is converted *in vivo* to tenofovir, a nucleoside monophosphate (nucleotide) analogue of adenosine monophosphate. Both emtricitabine and tenofovir have activity that is specific to human immunodeficiency virus (HIV-1 and HIV-2) and hepatitis B virus.

Emtricitabine and tenofovir are phosphorylated by cellular enzymes to form emtricitabine triphosphate and tenofovir diphosphate, respectively. Both emtricitabine and tenofovir can be fully phosphorylated when combined together in cells. Emtricitabine triphosphate and tenofovir diphosphate competitively inhibit HIV-1 reverse transcriptase, resulting in DNA chain termination.

Both emtricitabine triphosphate and tenofovir diphosphate are weak inhibitors of mammalian DNA polymerases and there was no evidence of toxicity to mitochondria *in vitro* and *in vivo*.

Antiviral activity *in vitro*

Synergistic antiviral activity was observed with the combination of emtricitabine and tenofovir *in vitro*. Additive to synergistic effects were observed with protease inhibitors, and with nucleoside and non-nucleoside analogue inhibitors of HIV reverse transcriptase.

Resistance

*In vitro:* Resistance has been seen *in vitro* and in some HIV-1 infected patients due to the development of the M184V/I mutation with emtricitabine or the K65R mutation with tenofovir. Emtricitabine-resistant viruses with the M184V/I mutation were cross-resistant to lamivudine, but retained sensitivity to didanosine, stavudine, tenofovir and zidovudine. The K65R mutation can also be selected by abacavir or didanosine and results in reduced susceptibility to

these agents plus lamivudine, emtricitabine and tenofovir. Tenofovir disoproxil should be avoided in patients with HIV-1 harbouring the K65R mutation. In addition, a K70E substitution in HIV-1 reverse transcriptase has been selected by tenofovir and results in low-level reduced susceptibility to abacavir, emtricitabine, lamivudine and tenofovir. HIV-1 expressing three or more thymidine analogue associated mutations (TAMs) that included either the M41L or L210W reverse transcriptase mutation showed reduced susceptibility to tenofovir disoproxil.

Paediatric population

The safety and efficacy of Tenohope E in children under the age of 12 years have not been established.

*Treatment of HIV-1 infection in the paediatric population*

There are no clinical studies conducted with Tenohope E in the paediatric population with HIV-1 infection.

*Pre-exposure prophylaxis in the paediatric population*

The efficacy and safety of Tenohope E for pre-exposure prophylaxis in adolescents who adhere to daily dosing is expected to be similar to that in adults at the same level of adherence. The potential renal and bone effects with long-term use of Tenohope E for pre-exposure prophylaxis in adolescents are unknown

**INDICATIONS:**
TENOHOPE-E is indicated in combination with other antiretroviral agents (such as non-nucleoside reverse transcriptase inhibitors or protease inhibitors) for the treatment of HIV-1 infection in adults.

The following points should be considered when initiating therapy with TENOHOPE-E for the treatment of HIV-1 infection:
-It is not recommended that TENOHOPE-E be used as a component of a triple nucleoside regimen.
-TENOHOPE-E should not be co-administered with lamivudine+ tenofovir DF+ Efavirenz, emtricitabine,tenofovir DF or lamivudine-containing products.
In treatment experienced patients, the use of TENOHOPE-E should be guided by laboratory testing and treatment history.

**CONTRAINDICATIONS:**
- Hypersensitivity to the active substances or to any of the excipients
- Use for pre-exposure prophylaxis in individuals with unknown or positive HIV-1 status.

**DOSAGE AND ADMINISTRATION**
The dosage of TENOHOPE-E is one tablet (containing 200 mg of emtricitabine and 300 mg of tenofovir DF) once daily taken orally with or without food.

Dose adjustment for renal impairment
Significantly increased drug exposures occurred when emtricitabine or tenofovir DF were administered to patients with moderate to severe renal impairment. Therefore, the dosing interval of TENOHOPE-E should be adjusted in patients with baseline creatinine clearance of 30-49 mL/min using the recommendations in Table 1. The safety and effectiveness of these dosing interval adjustment recommendations have not been clinically evaluated; therefore, clinical response to treatment and renal function should be closely monitored in these patients.
No dose adjustment is necessary for patients with mild renal impairment (creatinine clearance of 50 -80 mL/min). Routine monitoring of calculated creatinine clearance and serum phosphorus should be performed in patients with mild renal impairment.

Table 1: Dosage Adjustment for Patients with Altered Creatinine Clearance

| | Creatinine Clearance (mL/min)[a] | | |
|---|---|---|---|
| | ≥ 50 | 30–49 | < 30 (Including Patients Requiring Hemodialysis) |

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| Recommended Dosing Interval | Every 24 hours | Every 48 hours | Tenofovir + Emtricitabine Tablet should not be administered. |
| [a] Calculated using ideal (lean) body weight | | | |

**INTERACTIONS WITH OTHER MEDICAMENTS**
Interaction studies have only been performed in adults.

As Tenohope E contains emtricitabine and tenofovir disoproxil, any interactions that have been identified with these agents individually may occur with Tenohope E. Interaction studies have only been performed in adults.

The steady-state pharmacokinetics of emtricitabine and tenofovir were unaffected when emtricitabine and tenofovir disoproxil were administered together *versus* each medicinal product dosed alone.

It was shown that the potential for CYP450 mediated interactions involving emtricitabine and tenofovir disoproxil with other medicinal products is low.

Concomitant use not recommended

Tenohope E should not be administered concomitantly with other medicinal products containing emtricitabine, tenofovir disoproxil, tenofovir alafenamide or other cytidine analogues, such as lamivudine. Tenohope E should not be administered concomitantly with adefovir dipivoxil.

*Didanosine:* The co-administration of Tenohope E and didanosine is not recommended

*Renally eliminated medicinal products:* Since emtricitabine and tenofovir are primarily eliminated by the kidneys, co-administration of Tenohope E with medicinal products that reduce renal function or compete for active tubular secretion (e.g. cidofovir) may increase serum concentrations of emtricitabine, tenofovir and/or the co-administered medicinal products.

Use of Tenohope E should be avoided with concurrent or recent use of a nephrotoxic medicinal product. Some examples include, but are not limited to, aminoglycosides, amphotericin B, foscarnet, ganciclovir, pentamidine, vancomycin, cidofovir or interleukin-2

Other interactions

Interactions between Tenohope E or its individual component(s) and other medicinal products are listed in Table 2 below (increase is indicated as "↑", decrease as "↓", no change as "↔", twice daily as "b.i.d." and once daily as "q.d.").

Table 2: Interactions between Tenohope E or its individual component(s) and other medicinal products

| **Medicinal product by therapeutic areas** | **Effects on drug levels Change in AUC, $C_{max}$, $C_{min}$** | **Recommendation concerning co-administration with Tenohope E (emtricitabine 200 mg, tenofovir disoproxil 245 mg)** |
|---|---|---|
| ***ANTI-INFECTIVES*** | | |
| **Antiretrovirals** | | |
| **Protease inhibitors** | | |
| Atazanavir/Ritonavir/Tenofovir disoproxil (300 mg q.d./100 mg q.d./245 mg q.d.) | Atazanavir:<br>AUC: ↓<br>$C_{max}$: ↓<br>$C_{min}$: ↓<br>Tenofovir:<br>AUC: ↑<br>$C_{max}$: ↑<br>$C_{min}$: ↑ | No dose adjustment is recommended. The increased exposure of tenofovir could potentiate tenofovir associated adverse events, including renal disorders. Renal function should be closely monitored |
| Atazanavir/Ritonavir/Emtricitabine | Interaction not studied. | |
| Darunavir/Ritonavir/Tenofovir disoproxil | Darunavir: | No dose adjustment is recommended. The |

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| (300 mg q.d./100 mg q.d./245 mg q.d.) | AUC: ↔<br>$C_{min}$: ↔<br>Tenofovir:<br>AUC: ↑<br>$C_{min}$: ↑ | increased exposure of tenofovir could potentiate tenofovir associated adverse events, including renal disorders. Renal function should be closely monitored |
| Darunavir/Ritonavir/Emtricitabine | Interaction not studied. | |
| Lopinavir/Ritonavir/Tenofovir disoproxil (400 mg b.i.d./100 mg b.i.d/245 mg q.d.) | Lopinavir/Ritonavir:<br>AUC: ↔<br>$C_{max}$: ↔<br>$C_{min}$: ↔<br>Tenofovir:<br>AUC: ↑<br>$C_{max}$: ↔<br>$C_{min}$: ↑ | No dose adjustment is recommended. The increased exposure of tenofovir could potentiate tenofovir associated adverse events, including renal disorders. Renal function should be closely monitored |
| Lopinavir/Ritonavir/Emtricitabine | Interaction not studied. | |
| **NRTIs** | | |
| Didanosine/Tenofovir disoproxil | Co-administration of tenofovir disoproxil and didanosine results in a 40-60% increase in systemic exposure to didanosine that may increase the risk for didanosine-related adverse reactions. Rarely, pancreatitis and lactic acidosis, sometimes fatal, have been reported. Co-administration of tenofovir disoproxil and didanosine at a dose of 400 mg daily has been associated with a significant decrease in CD4 cell count, possibly due to an intracellular interaction increasing phosphorylated (i.e. active) didanosine. A decreased dosage of 250 mg didanosine co-administered with tenofovir disoproxil therapy has been associated with reports of high rates of virological failure within several tested combinations for the treatment of HIV-1 infection. | Co-administration of Tenohope E and didanosine is not recommended |
| Didanosine/Emtricitabine | Interaction not studied. | |
| Lamivudine/Tenofovir disoproxil | Lamivudine:<br>AUC: ↓<br>$C_{max}$: ↓<br>$C_{min}$: NC<br>Tenofovir:<br>AUC: ↓<br>$C_{max}$: ↑<br>$C_{min}$: NC | Lamivudine and Tenohope E should not be administered concomitantly |
| Efavirenz/Tenofovir disoproxil | Efavirenz:<br>AUC: ↓<br>$C_{max}$: ↓<br>$C_{min}$: NC<br>Tenofovir:<br>AUC: ↓<br>$C_{max}$: ↑<br>$C_{min}$: NC | No dose adjustment of efavirenz is required. |
| ***ANTI-INFECTIVES*** | | |

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| **Hepatitis B virus (HBV) antiviral agents** | | |
| Adefovir dipivoxil/Tenofovir disoproxil | Adefovir dipivoxil:<br>AUC: ↓<br>$C_{max}$: ↓<br>$C_{min}$: NC<br>Tenofovir:<br>AUC: ↓<br>$C_{max}$: ↓<br>$C_{min}$: NC | Adefovir dipivoxil and Tenohope E should not be administered concomitantly |
| **Hepatitis C virus (HCV) antiviral agents** | | |
| Ledipasvir/Sofosbuvir (90 mg/400 mg q.d.) + Atazanavir/Ritonavir (300 mg q.d./100 mg q.d.) + Emtricitabine/Tenofovir disoproxil (200 mg/245 mg q.d.)[1] | Ledipasvir:<br>AUC: ↑<br>$C_{max}$: ↑<br>$C_{min}$: ↑<br>Sofosbuvir:<br>AUC: ↔<br>$C_{max}$: ↔<br>GS-331007[2]:<br>AUC: ↔<br>$C_{max}$: ↔<br>$C_{min}$: ↑<br>Atazanavir:<br>AUC: ↔<br>$C_{max}$: ↔<br>$C_{min}$: ↑<br>Ritonavir:<br>AUC: ↔<br>$C_{max}$: ↔<br>$C_{min}$: ↑<br>Emtricitabine:<br>AUC: ↔<br>$C_{max}$: ↔<br>$C_{min}$: ↔<br>Tenofovir:<br>AUC: ↔<br>$C_{max}$: ↑<br>$C_{min}$: ↑ | Increased plasma concentrations of tenofovir resulting from co-administration of tenofovir disoproxil, ledipasvir/sofosbuvir and atazanavir/ritonavir may increase adverse reactions related to tenofovir disoproxil, including renal disorders. The safety of tenofovir disoproxil when used with ledipasvir/sofosbuvir and a pharmacokinetic enhancer (e.g. ritonavir or cobicistat) has not been established.<br>The combination should be used with caution with frequent renal monitoring, if other alternatives are not available |
| Ledipasvir/Sofosbuvir (90 mg/400 mg q.d.) + Darunavir/Ritonavir (800 mg q.d./100 mg q.d.) + Emtricitabine/Tenofovir disoproxil (200 mg/245 mg q.d.)[1] | Ledipasvir:<br>AUC: ↔<br>$C_{max}$: ↔<br>$C_{min}$: ↔<br>Sofosbuvir:<br>AUC: ↓<br>$C_{max}$: ↓<br>GS-331007[2]:<br>AUC: ↔<br>$C_{max}$: ↔<br>$C_{min}$: ↔<br>Darunavir:<br>AUC: ↔<br>$C_{max}$: ↔<br>$C_{min}$: ↔<br>Ritonavir:<br>AUC: ↔<br>$C_{max}$: ↔<br>$C_{min}$: ↑<br>Emtricitabine: | Increased plasma concentrations of tenofovir resulting from co-administration of tenofovir disoproxil, ledipasvir/sofosbuvir and darunavir/ritonavir may increase adverse reactions related to tenofovir disoproxil, including renal disorders. The safety of tenofovir disoproxil when used with ledipasvir/sofosbuvir and a pharmacokinetic enhancer (e.g. ritonavir or cobicistat) has not been established.<br>The combination should be used with caution with frequent renal monitoring, if other alternatives are not available |

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| | AUC: ↔<br>$C_{max}$: ↔<br>$C_{min}$: ↔<br>Tenofovir:<br>AUC: ↑<br>$C_{max}$: ↑<br>$C_{min}$: ↑ | |
| Ledipasvir/Sofosbuvir (90 mg/400 mg q.d.) + Efavirenz/Emtricitabine/Tenofovir disoproxil (600 mg/200 mg/245 mg q.d.) | Ledipasvir:<br>AUC: ↓<br>$C_{max}$: ↓<br>$C_{min}$: ↓<br>Sofosbuvir:<br>AUC: ↔<br>$C_{max}$: ↔<br>GS-331007[2]:<br>AUC: ↔<br>$C_{max}$: ↔<br>$C_{min}$: ↔<br>Efavirenz:<br>AUC: ↔<br>$C_{max}$: ↔<br>$C_{min}$: ↔<br>Emtricitabine:<br>AUC: ↔<br>$C_{max}$: ↔<br>$C_{min}$: ↔<br>Tenofovir:<br>AUC: ↑<br>$C_{max}$: ↑<br>$C_{min}$: ↑ | No dose adjustment is recommended. The increased exposure of tenofovir could potentiate adverse reactions associated with tenofovir disoproxil, including renal disorders. Renal function should be closely monitored |
| Ledipasvir/Sofosbuvir (90 mg/400 mg q.d.) + Emtricitabine/Rilpivirine/ Tenofovir disoproxil (200 mg/25 mg/245 mg q.d.) | Ledipasvir:<br>AUC: ↔<br>$C_{max}$: ↔<br>$C_{min}$: ↔<br>Sofosbuvir:<br>AUC: ↔<br>$C_{max}$: ↔<br>GS-331007[2]:<br>AUC: ↔<br>$C_{max}$: ↔<br>$C_{min}$: ↔<br>Emtricitabine:<br>AUC: ↔<br>$C_{max}$: ↔<br>$C_{min}$: ↔<br>Rilpivirine:<br>AUC: ↔<br>$C_{max}$: ↔<br>$C_{min}$: ↔<br>Tenofovir:<br>AUC: ↑<br>$C_{max}$: ↔<br>$C_{min}$: ↑ | No dose adjustment is recommended. The increased exposure of tenofovir could potentiate adverse reactions associated with tenofovir disoproxil, including renal disorders. Renal function should be closely monitored |
| Ledipasvir/Sofosbuvir (90 mg/400 mg q.d.) + Dolutegravir (50 mg q.d.) + Emtricitabine/Tenofovir disoproxil (200 mg/245 mg q.d.) | Sofosbuvir:<br>AUC: ↔<br>$C_{max}$: ↔<br>GS-331007[2] | No dose adjustment is required. The increased exposure of tenofovir could potentiate adverse reactions associated with tenofovir disoproxil, including renal |

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| | AUC: ↔<br>$C_{max}$: ↔<br>$C_{min}$: ↔<br>Ledipasvir:<br>AUC: ↔<br>$C_{max}$: ↔<br>$C_{min}$: ↔<br>Dolutegravir<br>AUC: ↔<br>$C_{max}$: ↔<br>$C_{min}$: ↔<br>Emtricitabine:<br>AUC: ↔<br>$C_{max}$: ↔<br>$C_{min}$: ↔<br>Tenofovir:<br>AUC: ↑<br>$C_{max}$: ↑<br>$C_{min}$: ↑ | disorders. Renal function should be closely monitored |
| Sofosbuvir/Velpatasvir (400 mg/100 mg q.d.) + Atazanavir/Ritonavir (300 mg q.d./100 mg q.d.) + Emtricitabine/Tenofovir disoproxil (200 mg/245 mg q.d.) | Sofosbuvir:<br>AUC: ↔<br>$C_{max}$: ↔<br>GS-331007[2]:<br>AUC: ↔<br>$C_{max}$: ↔<br>$C_{min}$: ↑<br>Velpatasvir:<br>AUC: ↑<br>$C_{max}$: ↑<br>$C_{min}$: ↑<br>Atazanavir:<br>AUC: ↔<br>$C_{max}$: ↔<br>$C_{min}$: ↑<br>Ritonavir:<br>AUC: ↔<br>$C_{max}$: ↔<br>$C_{min}$: ↑<br>Emtricitabine:<br>AUC: ↔<br>$C_{max}$: ↔<br>$C_{min}$: ↔<br>Tenofovir:<br>AUC: ↔<br>$C_{max}$: ↑<br>$C_{min}$: ↑ | Increased plasma concentrations of tenofovir resulting from co-administration of tenofovir disoproxil, sofosbuvir/velpatasvir and atazanavir/ritonavir may increase adverse reactions related to tenofovir disoproxil, including renal disorders. The safety of tenofovir disoproxil when used with sofosbuvir/velpatasvir and a pharmacokinetic enhancer (e.g. ritonavir or cobicistat) has not been established.<br>The combination should be used with caution with frequent renal monitoring |
| Sofosbuvir/Velpatasvir (400 mg/100 mg q.d.) + Darunavir/Ritonavir (800 mg q.d./100 mg q.d.) + Emtricitabine/Tenofovir disoproxil (200 mg/245 mg q.d.) | Sofosbuvir:<br>AUC: ↓<br>$C_{max}$: ↓<br>GS-331007[2]:<br>AUC: ↔<br>$C_{max}$: ↔<br>$C_{min}$: ↔<br>Velpatasvir:<br>AUC: ↔<br>$C_{max}$: ↓<br>$C_{min}$: ↔ | Increased plasma concentrations of tenofovir resulting from co-administration of tenofovir disoproxil, sofosbuvir/velpatasvir and darunavir/ritonavir may increase adverse reactions related to tenofovir disoproxil, including renal disorders. The safety of tenofovir disoproxil when used with sofosbuvir/velpatasvir and a pharmacokinetic enhancer (e.g. ritonavir or cobicistat) has not been established.<br>The combination should be used with caution |

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| | Darunavir:<br>AUC: ↔<br>$C_{max}$: ↔<br>$C_{min}$: ↔<br>Ritonavir:<br>AUC: ↔<br>$C_{max}$: ↔<br>$C_{min}$: ↔<br>Emtricitabine:<br>AUC: ↔<br>$C_{max}$: ↔<br>$C_{min}$: ↔<br>Tenofovir:<br>AUC: ↑<br>$C_{max}$: ↑<br>$C_{min}$: ↑ | with frequent renal monitoring |
| Sofosbuvir/Velpatasvir (400 mg/100 mg q.d.) + Lopinavir/Ritonavir (800 mg/200 mg q.d.) + Emtricitabine/Tenofovir disoproxil (200 mg/245 mg q.d.) | Sofosbuvir:<br>AUC: ↓<br>$C_{max}$: ↓<br>GS-331007[2]:<br>AUC: ↔<br>$C_{max}$: ↔<br>$C_{min}$: ↔<br>Velpatasvir:<br>AUC: ↔<br>$C_{max}$: ↓<br>$C_{min}$: ↑<br>Lopinavir:<br>AUC: ↔<br>$C_{max}$: ↔<br>$C_{min}$: ↔<br>Ritonavir:<br>AUC: ↔<br>$C_{max}$: ↔<br>$C_{min}$: ↔<br>Emtricitabine:<br>AUC: ↔<br>$C_{max}$: ↔<br>$C_{min}$: ↔<br>Tenofovir:<br>AUC: ↔<br>$C_{max}$: ↑<br>$C_{min}$: ↔ | Increased plasma concentrations of tenofovir resulting from co-administration of tenofovir disoproxil, sofosbuvir/velpatasvir and lopinavir/ritonavir may increase adverse reactions related to tenofovir disoproxil, including renal disorders. The safety of tenofovir disoproxil when used with sofosbuvir/velpatasvir and a pharmacokinetic enhancer (e.g. ritonavir or cobicistat) has not been established.<br>The combination should be used with caution with frequent renal monitoring |
| Sofosbuvir/Velpatasvir (400 mg/100 mg q.d.) + Raltegravir (400 mg b.i.d) + Emtricitabine/Tenofovir disoproxil (200 mg/245 mg q.d.) | Sofosbuvir:<br>AUC: ↔<br>$C_{max}$: ↔<br>GS-331007[2]:<br>AUC: ↔<br>$C_{max}$: ↔<br>$C_{min}$: ↔<br>Velpatasvir:<br>AUC: ↔<br>$C_{max}$: ↔<br>$C_{min}$: ↔<br>Raltegravir:<br>AUC: ↔<br>$C_{max}$: ↔ | No dose adjustment is recommended. The increased exposure of tenofovir could potentiate adverse reactions associated with tenofovir disoproxil, including renal disorders. Renal function should be closely monitored |

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| | $C_{min}$: ↓<br>Emtricitabine:<br>AUC: ↔<br>$C_{max}$: ↔<br>$C_{min}$: ↔<br>Tenofovir:<br>AUC: ↑<br>$C_{max}$: ↑<br>$C_{min}$: ↑ | |
| Sofosbuvir/Velpatasvir (400 mg/100 mg q.d.) + Efavirenz/Emtricitabine/Tenofovir disoproxil (600 mg/200 mg/245 mg q.d.) | Sofosbuvir:<br>AUC: ↔<br>$C_{max}$: ↑<br>GS-331007[2]:<br>AUC: ↔<br>$C_{max}$: ↔<br>$C_{min}$: ↔<br>Velpatasvir:<br>AUC: ↓<br>$C_{max}$: ↓<br>$C_{min}$: ↓<br>Efavirenz:<br>AUC: ↔<br>$C_{max}$: ↔<br>$C_{min}$: ↔<br>Emtricitabine:<br>AUC: ↔<br>$C_{max}$: ↔<br>$C_{min}$: ↔<br>Tenofovir:<br>AUC: ↑<br>$C_{max}$: ↑<br>$C_{min}$: ↑) | Concomitant administration of sofosbuvir/velpatasvir and efavirenz is expected to decrease plasma concentrations of velpatasvir. Co-administration of sofosbuvir/velpatasvir with efavirenz-containing regimens is not recommended. |
| Sofosbuvir/Velpatasvir (400 mg/100 mg q.d.) + Emtricitabine/Rilpivirine/Tenofovir disoproxil (200 mg/25 mg/245 mg q.d.) | Sofosbuvir:<br>AUC: ↔<br>$C_{max}$: ↔<br>GS-331007[2]:<br>AUC: ↔<br>$C_{max}$: ↔<br>$C_{min}$: ↔<br>Velpatasvir:<br>AUC: ↔<br>$C_{max}$: ↔<br>$C_{min}$: ↔<br>Emtricitabine:<br>AUC: ↔<br>$C_{max}$: ↔<br>$C_{min}$: ↔<br>Rilpivirine:<br>AUC: ↔<br>$C_{max}$: ↔<br>$C_{min}$: ↔<br>Tenofovir:<br>AUC: ↑<br>$C_{max}$: ↑<br>$C_{min}$: ↑ | No dose adjustment is recommended. The increased exposure of tenofovir could potentiate adverse reactions associated with tenofovir disoproxil, including renal disorders. Renal function should be closely monitored |
| Sofosbuvir/Velpatasvir/ Voxilaprevir (400 mg/100 mg/ 100 mg+100 mg | Sofosbuvir:<br>AUC: ↔ | Increased plasma concentrations of tenofovir resulting from co-administration of tenofovir |

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| q.d.)[3] + Darunavir (800 mg q.d.) + Ritonavir (100 mg q.d.) + Emtricitabine/Tenofovir disoproxil (200 mg/245 mg q.d.) | $C_{max}$: ↓<br>$C_{min}$: N/A<br>GS-331007[2]:<br>AUC: ↔<br>$C_{max}$:↔<br>$C_{min}$: N/A<br>Velpatasvir:<br>AUC: ↔<br>$C_{max}$: ↔<br>$C_{min}$: ↔<br>Voxilaprevir:<br>AUC: ↑<br>$C_{max}$:↑<br>$C_{min}$: ↑<br>Darunavir:<br>AUC: ↔<br>$C_{max}$: ↔<br>$C_{min}$: ↓<br>Ritonavir:<br>AUC: ↑<br>$C_{max}$: ↑<br>$C_{min}$: ↔<br>Emtricitabine:<br>AUC: ↔<br>$C_{max}$: ↔<br>$C_{min}$: ↔<br>Tenofovir:<br>AUC: ↑<br>$C_{max}$: ↑<br>$C_{min}$: ↑ | disoproxil, sofosbuvir/velpatasvir/voxilaprevir and darunavir/ritonavir may increase adverse reactions related to tenofovir disoproxil, including renal disorders. The safety of tenofovir disoproxil when used with sofosbuvir/velpatasvir/voxilaprevir and a pharmacokinetic enhancer (e.g. ritonavir or cobicistat) has not been established.<br>The combination should be used with caution with frequent renal monitoring |
| Sofosbuvir (400 mg q.d.) + Efavirenz/Emtricitabine/Tenofovir disoproxil (600 mg/200 mg/245 mg q.d.) | Sofosbuvir:<br>AUC: ↔<br>$C_{max}$: ↓<br>GS-331007[2]:<br>AUC: ↔<br>$C_{max}$: ↓<br>Efavirenz:<br>AUC: ↔<br>$C_{max}$: ↔<br>$C_{min}$: ↔<br>Emtricitabine:<br>AUC: ↔<br>$C_{max}$: ↔<br>$C_{min}$: ↔<br>Tenofovir:<br>AUC: ↔<br>$C_{max}$: ↑<br>$C_{min}$: ↔ | No dose adjustment is required. |
| Ribavirin/Tenofovir disoproxil | Ribavirin:<br>AUC: ↑<br>$C_{max}$: ↓<br>$C_{min}$: NC | No dose adjustment of ribavirin is required. |
| **Herpes virus antiviral agents** | | |
| Famciclovir/Emtricitabine | Famciclovir:<br>AUC: ↓<br>$C_{max}$: ↓<br>$C_{min}$: NC | No dose adjustment of famciclovir is required. |

| | | |
|---|---|---|
| | Emtricitabine:<br>AUC: ↓<br>$C_{max}$: ↓<br>$C_{min}$: NC | |
| **Antimycobacterials** | | |
| Rifampicin/Tenofovir disoproxil | Tenofovir:<br>AUC: ↓<br>$C_{max}$: ↓<br>$C_{min}$: ↓ | No dose adjustment is required. |
| ***ORAL CONTRACEPTIVES*** | | |
| Norgestimate/Ethinyl oestradiol/Tenofovir disoproxil | Norgestimate:<br>AUC: ↓<br>$C_{max}$: ↓<br>$C_{min}$: NC<br>Ethinyl oestradiol:<br>AUC: ↓<br>$C_{max}$: ↓<br>$C_{min}$: ↓ | No dose adjustment of norgestimate/ethinyl oestradiol is required. |
| ***IMMUNOSUPPRESSANTS*** | | |
| Tacrolimus/Tenofovir disoproxil/Emtricitabine | Tacrolimus:<br>AUC: ↑<br>$C_{max}$: ↑<br>$C_{min}$: NC<br>Emtricitabine:<br>AUC: ↓<br>$C_{max}$: ↓<br>$C_{min}$: NC<br>Tenofovir:<br>AUC: ↑<br>$C_{max}$: ↑<br>$C_{min}$: NC | No dose adjustment of tacrolimus is required. |
| ***NARCOTIC ANALGESICS*** | | |
| Methadone/Tenofovir disoproxil | Methadone:<br>AUC: ↑<br>$C_{max}$: ↑<br>$C_{min}$: NC | No dose adjustment of methadone is required. |

NC = not calculated.

[1] Simultaneous dosing with ledipasvir/sofosbuvir. Staggered administration (12 hours apart) provided similar results.

[2] The predominant circulating metabolite of sofosbuvir.

**WARNINGS & PRECAUTIONS**

Transmission of HIV

While effective viral suppression with antiretroviral therapy has been proven to substantially reduce the risk of sexual transmission, a residual risk cannot be excluded. Precautions to prevent transmission of HIV by infected individuals should be taken in accordance with national guidelines.

Patients with HIV-1 harbouring mutations

Tenohope E should be avoided in antiretroviral-experienced patients with HIV-1 harbouring the K65R mutation

Overall HIV-1 infection prevention strategy

Tenohope E is not always effective in preventing the acquisition of HIV-1. The time to onset of protection after commencing Tenohope E is unknown.

Tenohope E should only be used for pre-exposure prophylaxis as part of an overall HIV-1 infection prevention strategy including the use of other HIV-1 prevention measures (e.g. consistent and correct condom use, knowledge of HIV-1 status, regular testing for other sexually transmitted infections).

*Risk of resistance with undetected HIV-1 infection:*

Tenohope E should only be used to reduce the risk of acquiring HIV-1 in individuals confirmed to be HIV negative. Individuals should be re-confirmed to be HIV-negative at frequent intervals (e.g. at least every 3 months) using a combined antigen/antibody test while taking Tenohope E for pre-exposure prophylaxis.

Tenohope E alone does not constitute a complete regimen for the treatment of HIV-1 and HIV-1 resistance mutations have emerged in individuals with undetected HIV-1 infection who are only taking Tenohope E.

If clinical symptoms consistent with acute viral infection are present and recent (< 1 month) exposures to HIV-1 are suspected, use of Tenohope E should be delayed for at least one month and HIV-1 status reconfirmed before starting Tenohope E for pre-exposure prophylaxis.

*Importance of adherence:*

The effectiveness of Tenohope E in reducing the risk of acquiring HIV-1 is strongly correlated with adherence as demonstrated by measurable drug levels in blood. HIV-1 uninfected individuals should be counselled at frequent intervals to strictly adhere to the recommended Tenohope E daily dosing schedule.

Patients with hepatitis B or C virus infection

HIV-1 infected patients with chronic hepatitis B or C treated with antiretroviral therapy are at an increased risk for severe and potentially fatal hepatic adverse reactions. Physicians should refer to current HIV treatment guidelines for the management of HIV infection in patients co-infected with hepatitis B virus (HBV) or hepatitis C virus (HCV).

The safety and efficacy of Tenohope E for pre-exposure prophylaxis in patients with HBV or HCV infection has not been established.

In case of concomitant antiviral therapy for hepatitis B or C, please refer also to the relevant Summary of Product Characteristics for these medicinal products.

Tenofovir disoproxil is indicated for the treatment of HBV and emtricitabine has shown activity against HBV in pharmacodynamic studies but the safety and efficacy of Tenohope E have not been specifically established in patients with chronic HBV infection.

Discontinuation of Tenohope E therapy in patients infected with HBV may be associated with severe acute exacerbations of hepatitis. Patients infected with HBV who discontinue Tenohope E should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment. 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 disease

The safety and efficacy of Tenohope E have not been established in patients with significant underlying liver disorders. The pharmacokinetics of tenofovir has been studied in patients with hepatic impairment and no dose adjustment is required. The pharmacokinetics of emtricitabine has not been studied in patients with hepatic impairment. Based on minimal hepatic metabolism and the renal route of elimination for emtricitabine, it is unlikely that a dose adjustment would be required for Tenohope E in patients with hepatic impairment

HIV-1 infected patients with pre-existing liver dysfunction, including chronic active hepatitis, have an increased frequency of liver function abnormalities during combination antiretroviral therapy (CART) and should be monitored according to standard practice. If there is evidence of worsening liver disease in such patients, interruption or discontinuation of treatment must be considered.

Renal and bone effects in adults

*Renal effects*

Emtricitabine and tenofovir are primarily excreted by the kidneys by a combination of glomerular filtration and active tubular secretion. Renal failure, renal impairment, elevated creatinine, hypophosphataemia and proximal tubulopathy (including Fanconi syndrome) have been reported with the use of tenofovir disoproxil

*Renal monitoring*

Prior to initiating Tenohope E for the treatment of HIV-1 infection or for use in pre-exposure prophylaxis, it is recommended that creatinine clearance is calculated in all individuals.

In individuals without risk factors for renal disease, it is recommended that renal function (creatinine clearance and serum phosphate) is monitored after two to four weeks of use, after three months of use and every three to six months thereafter.

In individuals at risk for renal disease more frequent monitoring of renal function is required.

*Renal management in HIV-1 infected patients*

If serum phosphate is < 1.5 mg/dL (0.48 mmol/L) or creatinine clearance is decreased to < 50 mL/min in any patient receiving Tenohope E, renal function should be re-evaluated within one week, including measurements of blood glucose, blood potassium and urine glucose concentrations. Consideration should be given to interrupting treatment with Tenohope E in patients with creatinine clearance decreased to < 50 mL/min or decreases in serum phosphate to < 1.0 mg/dL (0.32 mmol/L). Interrupting treatment with Tenohope E should also be considered in case of progressive decline of renal function when no other cause has been identified.

Renal safety with Tenohope E has only been studied to a very limited degree in HIV-1 infected patients with impaired renal function (creatinine clearance < 80 mL/min). Dose interval adjustments are recommended for HIV-1 infected patients with creatinine clearance 30-49 mL/min. Limited clinical study data suggest that the prolonged dose interval is not optimal and could result in increased toxicity and possibly inadequate response. Furthermore, in a small clinical study, a subgroup of patients with creatinine clearance between 50 and 60 mL/min who received tenofovir disoproxil in combination with emtricitabine every 24 hours had a 2-4-fold higher exposure to tenofovir and worsening of renal function. Therefore, a careful benefit-risk assessment is needed when Tenohope E is used in patients with creatinine clearance < 60 mL/min, and renal function should be closely monitored. In addition, the clinical response to treatment should be closely monitored in patients receiving Tenohope E at a prolonged dosing interval. The use of Tenohope E is not recommended in patients with severe renal impairment (creatinine clearance < 30 mL/min) and in patients who require haemodialysis since appropriate dose reductions cannot be achieved with the combination tablet

*Renal management in pre-exposure prophylaxis*

Tenohope E has not been studied in HIV-1 uninfected individuals with creatinine clearance < 60 mL/min and is therefore not recommended for use in this population. If serum phosphate is < 1.5 mg/dL (0.48 mmol/L) or creatinine clearance is decreased to < 60 mL/min in any individual receiving Tenohope E for pre-exposure prophylaxis, renal function should be re-evaluated within one week, including measurements of blood glucose, blood potassium and urine glucose concentrations. Consideration should be given to interrupting use of Tenohope E in individuals with creatinine clearance decreased to < 60 mL/min or decreases in serum phosphate to < 1.0 mg/dL (0.32 mmol/L). Interrupting use of Tenohope E should also be considered in case of progressive decline of renal function when no other cause has been identified.

*Bone effects*

Bone abnormalities (infrequently contributing to fractures) may be associated with proximal renal tubulopathy. If bone abnormalities are suspected then appropriate consultation should be obtained.

*Treatment of HIV-1 infection*

The most pronounced decreases in BMD were seen in patients treated with tenofovir disoproxil as part of a regimen containing a boosted protease inhibitor. Alternative treatment regimens should be considered for patients with osteoporosis that are at a high risk for fractures.

*Pre-exposure prophylaxis*

In HIV-1 uninfected individuals, small decreases in BMD were observed.

Renal and bone effects in the paediatric population

There are uncertainties associated with the long-term renal and bone effects of tenofovir disoproxil during the treatment of HIV-1 infection in the paediatric population. There are no data on the long-term renal and bone effects of Tenohope E when used for pre-exposure prophylaxis in uninfected adolescents. Moreover, the reversibility of renal

toxicity after cessation of tenofovir disoproxil for treatment of HIV-1 or after cessation of Tenohope E for pre-exposure prophylaxis cannot be fully ascertained.

A multidisciplinary approach is recommended to weigh the benefit/risk balance of the use of Tenohope E for the treatment of HIV-1 infection or for pre-exposure prophylaxis, decide the appropriate monitoring during treatment (including decision for treatment withdrawal) and consider the need for supplementation on a case by case basis.

When using Tenohope E for pre-exposure prophylaxis individuals should be reassessed at each visit to ascertain whether they remain at high risk of HIV-1 infection. The risk of HIV-1 infection should be balanced against the potential for renal and bone effects with long-term use of Tenohope E.

*Renal effects*

Renal adverse reactions consistent with proximal renal tubulopathy have been reported in HIV-1 infected paediatric patients aged 2 to < 12 years

*Renal monitoring*

Renal function (creatinine clearance and serum phosphate) should be evaluated prior to initiating Tenohope E for treatment of HIV-1 or for pre-exposure prophylaxis and should be monitored during use as in adults

*Renal management*

If serum phosphate is confirmed to be < 3.0 mg/dL (0.96 mmol/L) in any paediatric patient receiving Tenohope E, renal function should be re-evaluated within one week, including measurements of blood glucose, blood potassium and urine glucose concentrations. If renal abnormalities are suspected or detected then consultation with a nephrologist should be obtained to consider interruption of Tenohope E use. Interrupting use of Tenohope E should also be considered in case of progressive decline of renal function when no other cause has been identified.

*Co-administration and risk of renal toxicity*

The same recommendations apply as in adults

*Renal impairment*

The use of Tenohope E is not recommended in individuals under the age of 18 years with renal impairment. Tenohope E should not be initiated in paediatric patients with renal impairment and should be discontinued in paediatric patients who develop renal impairment during Tenohope E use.

*Bone effects*

Use of tenofovir disoproxil may cause a reduction in BMD. The effects of tenofovir disoproxil-associated changes in BMD on long-term bone health and future fracture risk are currently unknown

If bone abnormalities are detected or suspected during use of Tenohope E in any paediatric patient, consultation with an endocrinologist and/or nephrologist should be obtained.

Weight and metabolic parameters

An increase in weight and in levels of blood lipids and glucose may occur during antiretroviral therapy. Such changes may in part be linked to disease control and life style. For lipids, there is in some cases evidence for a treatment effect, while for weight gain there is no strong evidence relating this to any particular treatment. For monitoring of blood lipids and glucose reference is made to established HIV treatment guidelines. Lipid disorders should be managed as clinically appropriate.

Mitochondrial dysfunction following exposure *in utero*

Nucleos(t)ide analogues may impact mitochondrial function to a variable degree, which is most pronounced with stavudine, didanosine and zidovudine. There have been reports of mitochondrial dysfunction in HIV negative infants exposed *in utero* and/or postnatally to nucleoside analogues; these have predominantly concerned treatment with regimens containing zidovudine. The main adverse reactions reported are haematological disorders (anaemia, neutropenia) and metabolic disorders (hyperlactatemia, hyperlipasemia). These events have often been transitory. Late onset neurological disorders have been reported rarely (hypertonia, convulsion, abnormal behaviour). Whether such neurological disorders are transient or permanent is currently unknown. These findings should be considered for any child exposed *in utero* to nucleos(t)ide analogues, who present with severe clinical findings of unknown etiology,

particularly neurologic findings. These findings do not affect current national recommendations to use antiretroviral therapy in pregnant women to prevent vertical transmission of HIV.

Immune Reactivation Syndrome

In HIV infected patients with severe immune deficiency at the time of institution of CART, an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first few weeks or months of initiation of CART. Relevant examples are cytomegalovirus retinitis, generalised and/or focal mycobacterial infections, and *Pneumocystis jirovecii* pneumonia. Any inflammatory symptoms should be evaluated and treatment instituted when necessary. Autoimmune disorders (such as Graves' disease and autoimmune hepatitis) have also been reported to occur in the setting of immune reactivation; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment.

Opportunistic infections

HIV-1 infected patients receiving Tenohope E or any other antiretroviral therapy may continue to develop opportunistic infections and other complications of HIV infection, and therefore should remain under close clinical observation by physicians experienced in the treatment of patients with HIV associated diseases.

Osteonecrosis

Although the aetiology is considered to be multifactorial (including corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index), cases of osteonecrosis have been reported particularly in patients with advanced HIV-disease and/or long-term exposure to CART. Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement.

Co-administration of other medicinal products

Use of Tenohope E should be avoided with concurrent or recent use of a nephrotoxic medicinal product. If concomitant use with nephrotoxic agents is unavoidable, renal function should be monitored weekly.

Cases of acute renal failure after initiation of high dose or multiple non-steroidal anti-inflammatory drugs (NSAIDs) have been reported in HIV-1 infected patients treated with tenofovir disoproxil and with risk factors for renal dysfunction. If Tenohope E is co-administered with an NSAID, renal function should be monitored adequately.

A higher risk of renal impairment has been reported in HIV-1 infected patients receiving tenofovir disoproxil in combination with a ritonavir or cobicistat boosted protease inhibitor. Close monitoring of renal function is required in these patients. In HIV-1 infected patients with renal risk factors, the co-administration of tenofovir disoproxil with a boosted protease inhibitor should be carefully evaluated.

Tenohope E should not be administered concomitantly with other medicinal products containing emtricitabine, tenofovir disoproxil, tenofovir alafenamide, or other cytidine analogues, such as lamivudine. Tenohope E should not be administered concomitantly with adefovir dipivoxil.

*Use with ledipasvir and sofosbuvir, sofosbuvir and velpatasvir or sofosbuvir, velpatasvir and voxilaprevir*

Co-administration of tenofovir disoproxil with ledipasvir/sofosbuvir, sofosbuvir/velpatasvir or sofosbuvir/velpatasvir/voxilaprevir has been shown to increase plasma concentrations of tenofovir, especially when used together with an HIV regimen containing tenofovir disoproxil and a pharmacokinetic enhancer (ritonavir or cobicistat).

The safety of tenofovir disoproxil when co-administered with ledipasvir/sofosbuvir, sofosbuvir/velpatasvir or sofosbuvir/velpatasvir/voxilaprevir and a pharmacokinetic enhancer has not been established. The potential risks and benefits associated with co-administration should be considered, particularly in patients at increased risk of renal dysfunction. Patients receiving ledipasvir/sofosbuvir, sofosbuvir/velpatasvir or sofosbuvir/velpatasvir/voxilaprevir concomitantly with tenofovir disoproxil and a boosted HIV protease inhibitor should be monitored for adverse reactions related to tenofovir disoproxil.

*Co-administration of tenofovir disoproxil and didanosine*

Co-administration is not recommended because it results in a 40-60% increase in systemic exposure to didanosine that may increase the risk of didanosine-related adverse reactions. Rarely, pancreatitis and lactic acidosis, sometimes fatal, have been reported. Co-administration of tenofovir disoproxil and didanosine at a dose of 400 mg daily has been

associated with a significant decrease in CD4 cell count, possibly due to an intracellular interaction increasing phosphorylated (i.e. active) didanosine. A decreased dosage of 250 mg didanosine co-administered with tenofovir disoproxil therapy has been associated with reports of high rates of virological failure within several tested combinations.

Triple nucleoside therapy

There have been reports of a high rate of virological failure and of emergence of resistance at an early stage in HIV-1 infected patients when tenofovir disoproxil was combined with lamivudine and abacavir as well as with lamivudine and didanosine as a once daily regimen. There is close structural similarity between lamivudine and emtricitabine and similarities in the pharmacokinetics and pharmacodynamics of these two agents. Therefore, the same problems may be seen if Tenohope E is administered with a third nucleoside analogue.

Elderly

Tenohope E has not been studied in individuals over the age of 65 years. Individuals over the age of 65 years are more likely to have decreased renal function, therefore caution should be exercised when administering Tenohope E to older people.

Excipients

Tenohope E contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency, or glucose-galactose malabsorption should not take this medicinal product.

**PREGNANCY:**

Pregnancy

A large amount of data on pregnant women (more than 1,000 pregnancy outcomes) indicate no malformations or foetal/neonatal toxicity associated with emtricitabine and tenofovir disoproxil. Animal studies on emtricitabine and tenofovir disoproxil do not indicate reproductive toxicity. Therefore the use of Tenohope E may be considered during pregnancy, if necessary.

Breast-feeding

Emtricitabine and tenofovir have been shown to be excreted in human milk. There is insufficient information on the effects of emtricitabine and tenofovir in newborns/infants. Therefore Tenohope E should not be used during breast-feeding.

As a general rule, it is recommended that HIV infected women do not breast-feed their infants under any circumstances in order to avoid transmission of HIV to the infant.

Fertility

No human data on the effect of Tenohope E are available. Animal studies do not indicate harmful effects of emtricitabine or tenofovir disoproxil on fertility.

**SIDE EFFECTS**

Frequencies are defined as very common, common, uncommon or rare.

| **Frequency** | **Emtricitabine** | **Tenofovir disoproxil fumarate** |
|---|---|---|
| *Blood and lymphatic system disorders:* | | |
| Common: | neutropenia | |
| Uncommon: | anaemia | |
| *Immune system disorders:* | | |
| Common: | allergic reaction | |
| *Metabolism and nutrition disorders:* | | |
| Very common: | | hypophosphataemia |
| Common: | hyperglycaemia, hypertriglyceridaemia | |
| Uncommon: | | hypokalaemia |

| | | |
|---|---|---|
| Rare: | | lactic acidosis |
| *Psychiatric disorders:* | | |
| Common: | insomnia, abnormal dreams | |
| *Nervous system disorders:* | | |
| Very common: | headache | dizziness |
| Common: | dizziness | headache |
| *Gastrointestinal disorders:* | | |
| Very common: | diarrhoea, nausea | diarrhoea, vomiting, nausea |
| Common: | Elevated amylase including elevated pancreatic amylase, elevated serum lipase, vomiting, abdominal pain, dyspepsia | abdominal pain, abdominal distension, flatulence |
| Uncommon: | | pancreatitis |
| *Hepatobiliary disorders:* | | |
| Common: | Elevated serum aspartate aminotransferase (AST) and/or elevated serum alanine aminotransferase (ALT), hyperbilirubinaemia | increased transaminases |
| Rare: | | hepatic steatosis, hepatitis |
| *Skin and subcutaneous tissue disorders:* | | |
| Very common: | | rash |
| Common: | vesiculobullous rash, pustular rash, maculopapular rash, rash, pruritus, urticaria, skin discolouration (increased pigmentation) | |
| Uncommon: | angioedema | |
| Rare: | | angioedema |
| *Musculoskeletal and connective tissue disorders:* | | |
| Very common: | Elevated creatine kinase | |
| Uncommon: | | rhabdomyolysis, muscular weakness |
| Rare: | | osteomalacia (manifested as bone pain and infrequently contributing to fractures), myopathy |
| *Renal and urinary disorders:* | | |
| Uncommon: | | increased creatinine, proteinuria, proximal renal tubulopathy including Fanconi syndrome |
| Rare: | | renal failure (acute and chronic), acute tubular necrosis, nephritis (including acute interstitial nephritis), nephrogenic diabetes insipidus |
| *General disorders and administration site conditions:* | | |
| Very common: | | asthenia |
| Common: | pain, asthenia | |

Description of selected adverse reactions

*Renal impairment:* As Tenohope E may cause renal damage monitoring of renal function is recommended. Proximal renal tubulopathy generally resolved or improved after tenofovir disoproxil discontinuation. However, in some HIV-1 infected patients, declines in creatinine clearance did not completely resolve despite tenofovir disoproxil discontinuation. Patients at risk of renal impairment (such as patients with baseline renal risk factors, advanced HIV disease, or patients receiving concomitant nephrotoxic medications) are at increased risk of experiencing incomplete recovery of renal function despite tenofovir disoproxil discontinuation

*Interaction with didanosine:* Co-administration of tenofovir disoproxil and didanosine is not recommended as it results in a 40-60% increase in systemic exposure to didanosine that may increase the risk of didanosine-related adverse reactions. Rarely, pancreatitis and lactic acidosis, sometimes fatal, have been reported.

*Metabolic parameters:* Weight and levels of blood lipids and glucose may increase during antiretroviral therapy.

*Immune Reactivation Syndrome:* In HIV infected patients with severe immune deficiency at the time of initiation of CART, an inflammatory reaction to asymptomatic or residual opportunistic infections may arise. Autoimmune disorders (such as Graves' disease and autoimmune hepatitis) have also been reported; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment

*Osteonecrosis:* Cases of osteonecrosis have been reported, particularly in patients with generally acknowledged risk factors, advanced HIV disease or long-term exposure to CART. The frequency of this is unknown

Paediatric population

In addition to the adverse reactions reported in adults, anaemia and skin discolouration occurred more frequently in in paediatric patients than in adults

Reductions in BMD have been reported in paediatric patients.

Other special populations

*Individuals with renal impairment:* Since tenofovir disoproxil can cause renal toxicity, close monitoring of renal function is recommended in any adults with renal impairment receiving Tenohope E. The use of Tenohope E is not recommended in individuals under the age of 18 years with renal impairment

*HIV/HBV or HCV co-infected patients:* As would be expected in this patient population, elevations in AST and ALT occurred more frequently than in the general HIV infected population.

*Exacerbations of hepatitis after discontinuation of treatment:* In HBV infected patients, clinical and laboratory evidence of hepatitis have occurred after discontinuation of treatment

**OVERDOSAGE AND TREATMENT**

If overdose occurs the individual must be monitored for evidence of toxicity, and standard supportive treatment applied as necessary.

Up to 30% of the emtricitabine dose and approximately 10% of the tenofovir dose can be removed by haemodialysis. It is not known whether emtricitabine or tenofovir can be removed by peritoneal dialysis.

**EFFECTS ON ABILITY TO DRIVE AND USE MACHINE**

No studies on the effects on the ability to drive and use machines have been performed. However, individuals should be informed that dizziness has been reported during treatment with both emtricitabine and tenofovir disoproxil.

**STORAGE INSTRUCTIONS**
Store below30°C in a dry place and protect from light. Keep out of reach of children.

**PRESENTATION**
30 tablets in a 75 cc HDPE container with polypropylene child resistant closure and 3gm silica gel sachet. Such 1 container is packed in a carton along with pack insert

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