Hepatitis C virus 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: AUC: ↑ C_{max}: ↑ C_{min}: ↑ Sofosbuvir: AUC: ↔ C_{max}: ↔ GS-331007[2]: AUC: ↔ C_{max}: ↔ C_{min}: ↑ Atazanavir: AUC: ↔ C_{max}: ↔ C_{min}: ↑ Ritonavir: AUC: ↔ C_{max}: ↔ C_{min}: ↑ Emtricitabine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir: AUC: ↔ C_{max}: ↑ 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. 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: AUC: ↔ C_{max} ↔ C_{min}: ↔ Sofosbuvir: AUC: ↓ C_{max}: ↓ GS-331007[2]: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Darunavir: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Ritonavir: AUC: ↔ C_{max}: ↔ C_{min}: ↑ Emtricitabine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir: AUC: ↑ C_{max}: ↑ C_{min}: ↑	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. 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.) + Efavirenz/Emtricitabine/ Tenofovir disoproxil (600 mg/200 mg/ 245 mg q.d.)	Ledipasvir: AUC: ↓ C_{max}: ↓ C_{min}: ↓ Sofosbuvir: AUC: ↔ C_{max}: ↔ GS-331007[2]: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Efavirenz: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Emtricitabine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir: AUC: ↑ C_{max}: ↑ 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: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Sofosbuvir: AUC: ↔ C_{max}: ↔ GS-331007[2]: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Emtricitabine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Rilpivirine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir: AUC: ↑ C_{max}: ↔ 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: AUC: ↔ C_{max}: ↔ GS-331007[2]: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Ledipasvir: AUC: ↔ C_{max}: ↔ 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
	Dolutegravir AUC: ↔ C_{max}: ↔ C_{min}: ↔ Emtricitabine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir: AUC: ↑ C_{max}: ↑ C_{min}: ↑	
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: AUC: ↔ C_{max}: ↔ GS-331007[2]: AUC: ↔ C_{max}: ↔ C_{min}: ↑ Velpatasvir: AUC: ↑ C_{max}: ↑ C_{min}: ↑ Atazanavir: AUC: ↔ C_{max}: ↔ C_{min}: ↑ Ritonavir: AUC: ↔ C_{max}: ↔ C_{min}: ↑ Emtricitabine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir: AUC: ↔ C_{max}: ↑ 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. 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: AUC: ↓ C_{max}: ↓ GS-331007[2]: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Velpatasvir: AUC: ↔ C_{max}: ↓ C_{min}: ↔ Darunavir: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Ritonavir: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Emtricitabine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir: AUC: ↑ C_{max}: ↑ 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. The combination should be used with caution 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: AUC: ↓ C_{max}: ↓ GS-331007[2]: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Velpatasvir: AUC: ↔ C_{max}: ↓ C_{min}: ↑ Lopinavir: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Ritonavir: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Emtricitabine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir: AUC: ↔ C_{max}: ↑ 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. 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: AUC: ↔ C_{max}: ↔ GS-331007[2]: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Velpatasvir: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Raltegravir: AUC: ↔ C_{max}: ↔ C_{min}: ↓ Emtricitabine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir: AUC: ↑ C_{max}: ↑ 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 (400 mg/100 mg q.d.) + Efavirenz/Emtricitabine/ Tenofovir disoproxil (600 mg/200 mg/ 245 mg q.d.)	Sofosbuvir: AUC: ↔ C_{max}: ↑ C_{min}: ↔ GS-331007[2]: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Velpatasvir: AUC: ↓ C_{max}: ↓	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.
	C_{min}: ↓ Efavirenz: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Emtricitabine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir: AUC: ↑ C_{max}: ↑ C_{min}: ↑	
Sofosbuvir/Velpatasvir (400 mg/100 mg q.d.) + Emtricitabine/Rilpivirine/ Tenofovir disoproxil (200 mg/25 mg/245 mg q.d.)	Sofosbuvir: AUC: ↔ C_{max}: ↔ GS-331007[2]: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Velpatasvir: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Emtricitabine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Rilpivirine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir: AUC: ↑ C_{max}: ↑ 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 q.d.) + Darunavir (800 mg q.d.) + Ritonavir (100 mg q.d.) + Emtricitabine/Tenofovir disoproxil (200 mg/ 245 mg q.d.)	Sofosbuvir: AUC: ↔ C_{max}: ↓ C_{min}: N/A GS-331007[2]: AUC: ↔ C_{max}:↔ C_{min}: N/A Velpatasvir: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Voxilaprevir: AUC: ↑ C_{max}:↑ C_{min}: ↑ Darunavir: AUC: ↔ C_{max}: ↔ C_{min}: ↓ Ritonavir: AUC: ↑ C_{max}: ↑ C_{min}: ↔ Emtricitabine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir: AUC: ↑ C_{max}: ↑ C_{min}: ↑	Increased plasma concentrations of tenofovir resulting from co-administration oftenofovir disoproxil, sofosbuvir/velpatasvir/voxilaprevir and darunavir/ritonavir may increase adverse reactions related to tenofovir disoproxil, including renaldisorders. The safety of tenofovir disoproxil when used with sofosbuvir/velpatasvir/voxilapre vir and a pharmacokinetic enhancer (e.g. ritonavir or cobicistat) has not been established. 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: AUC: ↔ C_{max}: ↓ GS-331007[2]: AUC: ↔ C_{max}: ↓ Efavirenz: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Emtricitabine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir: AUC: ↔ C_{max}: ↑ C_{min}: ↔	No dose adjustment is required.

[1] Data generated from simultaneous dosing with ledipasvir/sofosbuvir. Staggered administration (12 hours apart) provided similar results.

[2]The predominant circulating metabolite of sofosbuvir.

Studies conducted with other medicinal products

There were no clinically significant pharmacokinetic interactions when tenofovir disoproxil was co-administered with emtricitabine, lamivudine, indinavir, efavirenz, nelfinavir, saquinavir (ritonavir boosted), methadone, ribavirin, rifampicin, tacrolimus, or the hormonal contraceptive norgestimate/ethinyl oestradiol.

Tenofovir disoproxil must be taken with food, as food enhances the bioavailability of tenofovir

13. PREGNANCY AND LACTATION

Pregnancy

A moderate amount of data on pregnant women (between 300-1,000 pregnancy outcomes) indicate no malformations or foetal/neonatal toxicity associated with tenofovir disoproxil fumarate. Animal studies do not indicate reproductive toxicity. The use of tenofovir disoproxil fumarate may be considered during pregnancy, if necessary.

Breast-feeding

Tenofovir has been shown to be excreted in human milk. There is insufficient information on the effects of tenofovir in newborns/infants. Therefore tenofovir disoproxil fumarate tablets should not be used during breast-feeding.

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

Fertility

There are limited clinical data with respect to the effect of tenofovir disoproxil fumarate on fertility. Animal studies do not indicate harmful effects of tenofovir disoproxil fumarate on fertility.

14. Undesirable effects

Summary of the safety profile

HIV-1 and hepatitis B: In patients receiving tenofovir disoproxil, rare events of renal impairment, renal failure and uncommon events of proximal renal tubulopathy (including Fanconi syndrome) sometimes leading to bone abnormalities (infrequently contributing to fractures) have been reported. Monitoring of renal function is recommended for patients receiving Tenolaurus (see section Warnings and Precautions).

HIV-1: Approximately one third of patients can be expected to experience adverse reactions following treatment with tenofovir disoproxil in combination with other antiretroviral agents. These reactions are usually mild to moderate gastrointestinal events.

Co-administration of Tenolaurus and didanosine is not recommended as this may result in an increased risk of adverse reactions (see section Interactions With Other Medicaments). Rarely, pancreatitis and lactic acidosis, sometimes fatal, have been reported (see section Warnings and Precautions).

Hepatitis B: Approximately one quarter of patients can be expected to experience adverse reactions following treatment with tenofovir disoproxil, most of which are mild such as nausea.

Acute exacerbation of hepatitis has been reported in patients on treatment as well as in patients who have discontinued hepatitis B therapy (see section Warnings and Precautions).

Tabulated summary of adverse reactions

All adverse reactions are presented in Table 3.

The adverse reactions with suspected (at least possible) relationship to treatment are listed below by body system organ class and frequency. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Frequencies are defined as very common, common, uncommon or rare

Table 3: Tabulated summary of adverse reactions associated with tenofovir disoproxil

Frequency	**Tenofovir disoproxil**
Metabolism and nutrition disorders:	
Very common:	hypophosphataemia[1]
Uncommon:	hypokalaemia[1]
Rare:	lactic acidosis
Nervous system disorders:	
Very common:	dizziness
Common:	headache
Gastrointestinal disorders:	
Very common:	diarrhoea, vomiting, nausea
Common:	abdominal pain, abdominal distension, flatulence
Uncommon:	pancreatitis
Hepatobiliary disorders:	
Common:	increased transaminases
Rare:	hepatic steatosis, hepatitis
Skin and subcutaneous tissue disorders:	
Very common:	rash
Rare:	angioedema
Musculoskeletal and connective tissue disorders:	
Uncommon:	rhabdomyolysis[1], muscular weakness[1]
Rare:	osteomalacia (manifested as bone pain and infrequently contributing to fractures)[1,2], myopathy[1]
Renal and urinary disorders:	
Uncommon:	increased creatinine, proximal renal tubulopathy (including Fanconi syndrome)
Rare:	acute renal failure, renal failure, acute tubular necrosis, nephritis (including acute interstitial nephritis)[2], nephrogenic diabetes insipidus
General disorders and administration site conditions:	
Very common:	asthenia
Common:	fatigue

[1] This adverse reaction may occur as a consequence of proximal renal tubulopathy. It is not considered to be causally associated with tenofovir disoproxil in the absence of this condition.

[2]This adverse reaction was identified through post-marketing surveillance

Description of selected adverse reactions

HIV-1 and hepatitis B:

Renal impairment

As Tenolaurus may cause renal damage monitoring of renal function is recommended (see sections Warnings and Precautions and Summary of the safety profile). Proximal renal tubulopathy generally resolved or improved after tenofovir disoproxil discontinuation. However, in some 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 (see section Warnings and Precautions).

HIV-1:

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 (see section Interactions With Other Medicaments). 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 (see section Warnings and Precautions).

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 (see section Warnings and Precautions).

Osteonecrosis

Cases of osteonecrosis have been reported, particularly in patients with generally acknowledged risk factors, advanced HIV disease or long-term exposure to CART. (see section Warnings and Precautions).

Hepatitis B:

Exacerbations of hepatitis during treatment

Periodic monitoring of hepatic function is recommended during treatment (see section Warnings and Precautions).

Exacerbations of hepatitis after discontinuation of treatment

In HBV infected patients, clinical and laboratory evidence of exacerbations of hepatitis have occurred after discontinuation of HBV therapy (see section Warnings and Precautions).

Paediatric population

HIV-1

The adverse reactions observed in paediatric patients who received treatment with tenofovir disoproxil were consistent with adults (see section Tabulated summary of adverse reactions and Pharmacodynamic properties).

Reductions in Bone Mineral Density (BMD) have been reported in paediatric patients.

Chronic hepatitis B

The adverse reactions observed in adolescent patients who received treatment with tenofovir disoproxil were consistent with adults (see section Tabulated summary of adverse reactions and Pharmacodynamic properties).

Reductions in BMD have been observed in HBV infected adolescents.

Other special population(s)

Elderly

Tenofovir disoproxil has not been studied in patients over the age of 65. Elderly patients are more likely to have decreased renal function, therefore caution should be exercised when treating elderly patients with tenofovir disoproxil (see section Warnings and Precautions).

Patients with renal impairment

Since tenofovir disoproxil can cause renal toxicity, close monitoring of renal function is recommended in adult patients with renal impairment treated with Tenolaurus (see sections Recommended Dose, Warnings and Precautions and Pharmacodynamic properties). The use of tenofovir disoproxil is not recommended in paediatric patients with renal impairment (see sections Recommended Dose and Warnings and Precautions).

15. OVERDOSE AND TREATMENT

Symptoms

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

Management

Tenofovir can be removed by haemodialysis; the median haemodialysis clearance of tenofovir is 134 ml/min. It is not known whether tenofovir can be removed by peritoneal dialysis.

16. STORAGE CONDITION

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

17. DOSAGE FORMS AND PACKAGING AVAILABLE

30's Count: White opaque 60 cc HDPE bottles filled with 1gm silica gel canister, polyester coil closed with 33 mm child resistant closures.

18. NAME AND ADDRESS OF PRODUCT REGISTRATION HOLDER

Synerrv Sdn Bhd

SO-29-2, MENARA 1, KL ECO CITY, JALAN BANGSAR, KG HAJI ABDULLAH HUKUM, 59200 KUALA LUMPUR, MALAYSIA.

Manufactured by:

M/s. Laurus Labs Limited (Unit-II), Plot No.:19, 20 & 21, Western Sector, APSEZ, Gurajapalem Village, Rambilli Mandal, Anakapalli District - 531011, Andhra Pradesh, India.

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