VELSO™

(Velpatasvir / Sofosbuvir) Tablets

100mg / 400mg

ویلسو ۱۰۰ ملی گرام/۴۰۰ ملی گرام ٹیبلٹس

DESCRIPTION:
VELSO is a fixed-dose combination of sofosbuvir, a hepatitis C virus (HCV) nucleotide analog NS5B polymerase inhibitor, and velpatasvir, an HCV NS5A inhibitor.The molecular formula of Sofosbuvir is $C_{22}H_{29}FN_3O_9P$ and its molecular weight is 529.453 g/mol. The molecular formula of Velpatasvir is $C_{49}H_{54}N_8O_8$ with a molecular weight 883.02 g/mol.

MECHANISM OF ACTION:
Sofosbuvir is an inhibitor of the HCV NS5B RNA-dependent RNA polymerase, which is required for viral replication. Sofosbuvir is a nucleotide prodrug that undergoes intracellular metabolism to form the pharmacologically active uridine analog triphosphate (GS-461203), which can be incorporated into HCV RNA by the NS5B polymerase and acts as a chain terminator. In a biochemical assay, GS-461203 inhibited the polymerase activity of the recombinant NS5B from HCV genotype 1b, 2a, 3a, and 4a with an IC50 value ranging from 0.36 to 3.3 micromolar. GS-461203 is neither an inhibitor of human DNA and RNA polymerases nor an inhibitor of mitochondrial RNA polymerase.
Velpatasvir is an inhibitor of the HCV NS5A protein, which is required for viral replication. Resistance selection in cell culture and cross-resistance studies indicate velpatasvir targets NS5A as its mode of action.

COMPOSITION:
Each film-coated tablet contains:
Velpatasvir.....100mg
Sofosbuvir..... 400mg
Innovator's Specs.

INDICATIONS AND USAGE:
VELSO Tablets are indicated for the treatment of adult patients with chronic hepatitis C virus (HCV) genotype 1, 2, 3, 4, 5, or 6 infections:
• without cirrhosis or with compensated cirrhosis
• with decompensated cirrhosis for use in combination with ribavirin

DOSAGE & ADMINISTRATION:
1 tablet per day.

Treatment duration: Patients without cirrhosis or with compensated cirrhosis (Child-Pugh A): Sofosbuvir/velpatasvir for 12 weeks. Patients with decompensated cirrhosis (Child-Pugh B or C): Sofosbuvir/velpatasvir plus weight-based ribavirin with food for 12 weeks.

Pharmacokinetics:
The pharmacokinetic properties of the components of VELSO are provided in table.

	SOFOSBUVIR	VELPATASVIR
Absorption		
Tmax (h)	0.5-1	3
Effect of moderate meal (relative to fasting)[a]	↑60%	↑↑
Effect of high fat meal (relative to fasting)[a]	↑78%	↑21%
Distribution		
% Bound to human plasma proteins	6165	>99.5
Blood-to-plasma ratio	0.7	0.52-0.67
Metabolism		
Metabolism	Cathepsin A	CYP2B6
	CES1	CYP2C8
	HINT1	CYP3A4
Elimination		
Major route of elimination	SOF:metabolismGS-331007:glomerularfiltration & active tubular secretion	Biliary excretion as parent (77%)
t½ (h)[c]	SOF: 0.5 GS-331007[b]: 25	15
% Of dose excreted in urine[d]	80[e]	0.4
% Of dose excreted in feces[d]	14	94

CES1 = carboxylesterase 1; HINT1 = histidine triad nucleotide-binding protein 1 a Values refer to mean systemic exposure. Moderate meal = ~600 kcal, 30% fat; high fat meal = ~800 kcal, 50% fat. EPCLUSA can be taken with or without food. b GS-331007 is the primary circulating nucleoside metabolite of SOF. c t½ values refer to median terminal plasma half-life. d Single dose administration of [14C] SOF or [14C] VEL in mass balance studies. e Predominantly as GS-331007.

USE IN SPECIFIC POPULATIONS:
PREGNANCY:
If VELSO Tablets are administered with ribavirin, the combination regimen is contraindicated in pregnant women and in men whose female partners are pregnant.

Nursing Mothers: It is not known whether the components of VELSO and its metabolites are present in human breast milk, affect human milk production, or have effects on the breastfed infant. If VELSO is administered with ribavirin, the nursing mother's information for ribavirin also applies to this combination regimen.

Pediatric Use: Safety and effectiveness of VELSO Tablets have not been established in pediatric patients.

Renal Impairment: No dosage adjustment of VELSO Tablets are required for patients with mild or moderate renal impairment.

Contraindications: VELSO and ribavirin combination regimen is contraindicated in patients for whom ribavirin is contraindicated

Warnings and Precautions: Bradycardia with amiodarone coadministration: Serious symptomatic bradycardia may occur in patients taking amiodarone, particularly in patients also receiving beta blockers, or those with underlying cardiac
comorbidities and/or advanced liver disease. Coadministration of amiodarone with VELSO Tablets is not recommended. In patients without alternative viable treatment options, cardiac monitoring is recommended.

SIDE EFFECTS: • The most common adverse reactions (incidence greater than or equal to 10%) observed with treatment with VELSO for 12 weeks are headache and fatigue.
• The most common adverse reactions (incidence greater than or equal to 10%) observed with treatment with VELSO and ribavirin for 12 weeks in patients with decompensated cirrhosis are fatigue, anemia, nausea, headache, insomnia, and diarrhea.

DRUG INTERACTIONS:
1. Potential for Other Drugs to Affect VELSO (Sofosbuvir) & velpatasvir are substrates of drug transporters P-gp and BCRP while GS-331007 (the predominant circulating metabolite of sofosbuvir) is not. In vitro, slow metabolic turnover of velpatasvir by CYP2B6, CYP2C8, and CYP3A4 was observed. Drugs that are inducers of P-gp and/or moderate to potent inducers of CYP2B6, CYP2C8, or CYP3A4 (e.g., rifampin, St. John's wort, carbamazepine) may decrease plasma concentrations of sofosbuvir and/or velpatasvir, leading to reduced therapeutic effect of VELSO. The use of these agents with VELSO is not recommended. VELSO may be coadministered with P-gp, BCRP, and CYP inhibitors.
2. Potential for VELSO to Affect Other Drugs Velpatasvir is an inhibitor of drug transporters P-gp, breast cancer resistance protein (BCRP), OATP1B1, OATP1B3, and OATP2B1. Coadministration of VELSO with drugs that are substrates of these transporters may increase the exposure of such drugs.
3. Established and Potentially Significant Drug Interactions Below table provides a listing of established or potentially clinically significant drug interactions.
Acid Reducing Agents: Velpatasvir solubility decreases as pH increases. Drugs that increase gastric pH are expected to decrease concentration of velpatasvir.
Separate antacid and VELSO administration by 4 hours.
H2-receptor antagonists ‡ (e.g., famotidine): H2 -receptor antagonists may be administered simultaneously with or 12 hours apart from VELSO at a dose that does not exceed doses comparable to famotidine 40 mg twice daily.
Antiarrhythmics: amiodarone: Coadministration of amiodarone with VELSO may result in serious symptomatic bradycardia. The mechanism of this effect is unknown. Coadministration of amiodarone with VELSO is not recommended; if coadministration is required, cardiac monitoring is recommended.
Digoxin: Therapeutic concentration monitoring of digoxin is recommended when coadministered with VELSO. Refer to digoxin prescribing information for monitoring and dose modification recommendations for concentration increases of less than 50%.
Anticancers: (Topotecan), **Anticonvulsants:** (carbamazepine,phenytoin,phenobarbital,oxcarbazepine), **Antimycobacterials:** (rifabutin,rifampin), **HIV Antiretrovirals:** (Efavirenz) Coadministration is not recommended.
Regimens containing tenofovir DF: Monitor for tenofovir-associated adverse reactions in patients receiving VELSO concomitantly with a regimen containing tenofovir DF. Refer to the prescribing information of the tenofovir DF-containing product for recommendations on renal monitoring.
Tipranavir/Ritonavir, Herbal Supplements: St. John's wort (Hypericum perforatum): Coadministration is not recommended.
HMG-CoA Reductase Inhibitors: rosuvastatin: Coadministration of VELSO with rosuvastatin may significantly increase the concentration of rosuvastatin, which is associated with increased risk of myopathy, including rhabdomyolysis. Rosuvastatin may be administered with VELSO at a dose that does not exceed 10 mg.
Atorvastatin: Coadministration of VELSO with atorvastatin is expected to increase the concentrations of atorvastatin, which is associated with increased risk of myopathy, including rhabdomyolysis. Monitor closely for HMG-CoA reductase inhibitor-associated adverse reactions, such as myopathy and rhabdomyolysis.
4. Drugs without Clinically Significant Interactions with VELSO Based on drug interaction studies conducted with the components of VELSO, no clinically significant drug interactions have been observed with the following drugs: • VELSO: atazanavir/ritonavir, cyclosporine, darunavir/ritonavir, dolutegravir, elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide, emtricitabine, raltegravir or rilpivirine • Sofosbuvir: ethinyl estradiol/norgestimate, methadone, or tacrolimus • Velpatasvir: ethinyl estradiol/norgestimate, ketoconazole, or pravastatin. See above Table for use of VELSO with certain HIV antiretroviral regimens.

OVERDOSE:
No specific antidote is available for overdose with VELSO. If overdose occurs the patient must be monitored for evidence of toxicity. Treatment of overdose with VELSO consists of general supportive measures including monitoring of vital signs as well as observation of the clinical status of the patient. Hemodialysis can efficiently remove the predominant circulating metabolite of sofosbuvir, GS-331007, with an extraction ratio of 53%. Hemodialysis is unlikely to result in significant removal of velpatasvir since velpatasvir is highly bound to plasma protein.

INSTRUCTIONS:
Dosage as directed by the physician.
Store below 30°C. Protect from heat, light & moisture.
Keep all medicines out of the reach of children.
To be sold on the prescription of a registered
medical practitioner only.

PRESENTATION:
VELSO™ (Velpatasvir / Sofosbuvir) 100mg/400mg tablets are available in ALU/ALU blister pack of 4x7's tablets with Leaflet.

علامات/طریقہ استعمال:

ویلسو ٹیبلٹس درج ذیل علامات میں استعمال کی جاتی ہیں۔

- دائمی ہیپاٹائٹس سی وائرس (ایچ سی وی) ۱، ۲، ۳، ۴، ۵ اور ۶ انفیکشن۔
- بغیر سرہوسس یا کمپنسیٹیڈ سرہوسس۔
- ڈی کمپنسیٹیڈ سرہوسس میں رباورن کے ساتھ۔

ایک ٹیبلٹ دن میں ایک مرتبہ۔ علاج کا دورانیہ ۱۲ ہفتوں پر مشتمل ہوسکتا ہے۔

مضر اثرات: سر درد، تھکن، خون کی کمی، متلی، دست اور نیند نہ آنا۔

احتیاطی تدابیر: امیڈرون کے ساتھ ویلسو ٹیبلٹس کا استعمال ممنوع ہے۔

ہدایات: ۳۰ ڈگری سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔
روشنی، گرمی اور نمی سے محفوظ رکھیں۔
تمام دوائیں بچوں کی پہنچ سے دور رکھیں۔
صرف رجسٹرڈ ڈاکٹر کے نسخہ پر فروخت کریں۔

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