Front

ABRIVA PLUS™ 400/100
(Sofosbuvir / Velpatasvir)
Tablet

ایبریوا پَلس

COMPOSITION:
Each film coated tablet contains:
Sofosbuvir ..... 400 mg.
Velpatasvir ..... 100 mg.

Product Specs.: Innovator

DESCRIPTION:
ABRIVA PLUS is a fixed-dose combination tablet containing sofosbuvir and velpatasvir for oral administration. Each tablet contains 400 mg sofosbuvir and 100 mg velpatasvir. Sofosbuvir is a nucleotide analog HCV NS5B polymerase inhibitor and velpatasvir is an NS5A inhibitor.
Sofosbuvir:
The IUPAC name for sofosbuvir is (S)-Isopropyl 2-((S)-(((2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-4-fluoro-3hydroxy-4-methyltetrahydrofuran-2yl)methoxy)(phenoxy)phosphorylamino)propanoate. It has a molecular formula of $C_{22}H_{29}FN_3O_9P$ and a molecular weight of 529.45.
Velpatasvir:
The IUPAC name for velpatasvir is Methyl {(1R)-2-[(2S,4S)-2-(5-{2-[(2S,5S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}-5-methylpyrrolidin-2-yl]-1,11-dihydro[2]benzopyrano[4',3':6,7]naphtho[1,2-d]imidazol-9-yl}-1H-imidazol-2-yl)-4-(methoxymethyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate. It has a molecular formula of $C_{49}H_{54}N_8O_8$ and a molecular weight of 883.0.

CLINICAL PHARMACOLOGY:
Mechanism of action:
ABRIVA PLUS is a fixed-dose combination of sofosbuvir and velpatasvir which are direct-acting antiviral agents against the hepatitis C virus.
Cardiac electrophysiology:
At a dose 3 times the recommended dose (1200 mg), sofosbuvir does not prolong QTc to any clinically relevant extent.
At a dose 5 times the recommended dose, velpatasvir does not prolong QTc interval to any clinically relevant extent.
Pharmacokinetics:
The pharmacokinetic properties of the components of ABRIVA PLUS are

	Sofosbuvir	**Velpatasvir**
Absorption		
T_{max} (h)	0.5–1 3	3
Effect of moderate meal (relative to fasting)[a]	↑ 60%	↑ 34%
Effect of high fat meal (relative to fasting)[a]	↑ 78%	↑ 21%
Distribution	61–65	>99.5
%Bound to human plasma proteins	0.7	0.52-0.67
Blood-to-plasma ratio		
Metabolism		
Metabolism	Cathepsin A	CYP2B6
	CES1	CYP2C8
	HINT1	CYP3A4
Elimination		
Major route of elimination	SOF: metabolism	
	GS-331007[b]: glomerular	Biliary excretion as parent
	filtration and active tubular	
	secretion	(77%)
t½ (h)[c]	SOF: 0.5	15
	GS-331007[b]: 25	
% 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. **ABRIVA PLUS** 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.
Specific Populations:
Pediatric patients:
The pharmacokinetics of sofosbuvir or velpatasvir in pediatric patients has not been established.
Patients with renal impairment:
The pharmacokinetics of sofosbuvir were studied in HCV negative subjects with mild (eGFR between 50 to less than 80 mL/min/1.73 m^2), moderate (eGFR between 30 to less than 50 mL/min/1.73 m^2), severe renal impairment (eGFR less than 30 mL/min/1.73 m^2), and subjects with ESRD requiring hemodialysis following a single 400 mg dose of sofosbuvir.
The pharmacokinetics of velpatasvir were studied with a single dose of 100 mg velpatasvir in HCV negative subjects with severe renal impairment (eGFR less than 30 mL/min by Cockcroft-Gault). No clinically relevant differences in velpatasvir pharmacokinetics were observed between healthy subjects and subjects with severe renal impairment.
Patients with hepatic impairment:
The pharmacokinetics of sofosbuvir were studied following 7-day dosing of 400 mg sofosbuvir in HCV-infected subjects with moderate and severe hepatic impairment (Child-Pugh Class B and C, respectively). Relative to subjects with normal hepatic function, the sofosbuvir AUC_{0-24} were 126% and 143% higher in moderate and severe hepatic impairment, while the GS-331007 AUC_{0-24} were 18% and 9% higher, respectively. Population pharmacokinetics analysis in HCV-infected subjects indicated that cirrhosis (including decompensated cirrhosis) had no clinically relevant effect on the exposure of sofosbuvir and GS-331007. The pharmacokinetics of velpatasvir were studied with a single dose of 100 mg velpatasvir in HCV negative subjects with moderate and severe hepatic impairment (Child-Pugh Class B and C). Velpatasvir plasma exposure (AUC_{inf}) was similar in subjects with moderate hepatic impairment, severe hepatic impairment, and control subjects with normal hepatic function. Population pharmacokinetics analysis in HCV-infected subjects indicated that cirrhosis (including decompensated cirrhosis) had no clinically relevant effect on the exposure of velpatasvir.
Race: No clinically relevant effect on the exposure of sofosbuvir, GS-331007, or velpatasvir.
Gender: Had no clinically relevant effect on the exposure of sofosbuvir, GS-331007, or velpatasvir.

INDICATIONS AND USAGE:
ABRIVA PLUS is indicated for the treatment of adult patients with chronic hepatitis C virus (HCV) genotype 1, 2, 3, 4, 5, or 6 infection:
- Without cirrhosis or with compensated cirrhosis.
- With decompensated cirrhosis for use in combination with ribavirin.

DOSAGE AND ADMINISTRATION:
Testing prior to the initiation of therapy:
Test all patients for evidence of current or prior HBV infection by measuring hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (anti-HBc) before initiating HCV treatment with **ABRIVA PLU**S.

RECOMMENDED DOSAGE:
The recommended dosage of **ABRIVA PLUS** is one tablet taken orally once daily with or without food. One tablet of **ABRIVA PLUS** contains 400 mg of sofosbuvir and 100 mg of velpatasvir

ADMINISTRATION:
Recommended treatment regimen and duration based on patient population are:

Patient Population	**Treatment Regimen and Duration**
Treatment-naïve and treatment-Experienced a, without cirrhosis and with compensated cirrhosis (Child-Pugh A)	**ABRIVA PLUS** 12 weeks
Treatment-naïve and treatment-Experienceda, with decompensated cirrhosis (Child-Pugh B or C)	**ABRIVA PLUS + ribavirin**[b] 12 weeks

a. In clinical trials, regimens contained peginterferon alfa/ribavirin with or without an HCV NS3/4A protease inhibitor (boceprevir, simeprevir, or telaprevir).
b. When administered with Sofosbuvir/Velpatasvir, the recommended dosage of ribavirin is based on weight (administered with food): 1000 mg per day for patients less than 75 kg and 1200 mg for those weighing at least 75 kg, divided and administered twice daily. The starting dosage and on-treatment dosage of ribavirin can be decreased based on hemoglobin and creatinine clearance. For ribavirin dosage modifications, refer to the ribavirin prescribing information.
When administered with ABRIVA PLUS the recommended dosage of ribavirin is based on weight (administered with food: 1000 mg per day for patients less than 75 kg and 1200 mg for those weighing at least 75 kg, divided and administered twice daily. The starting dosage and on-treatment dosage of ribavirin can be decreased based on hemoglobin and creatinine clearance. For ribavirin dosage modifications, refer to the ribavirin prescribing information.

DOSE MODIFICATION RECOMMENDATIONS:
No dosage recommendation can be given for patients with severe renal impairment (estimated Glomerular Filtration Rate [eGFR] less than 30 mL/min/1.73 m^2) or with end stage renal disease (ESRD), due to higher exposures (up to 20-fold) of the predominant sofosbuvir metabolite.

CONTRAINDICATIONS:
ABRIVA PLUS and ribavirin combination regimen is contraindicated in patients for whom ribavirin is contraindicated. Refer to the ribavirin prescribing information for a list of contraindications for ribavirin.

WARNINGS AND PRECAUTIONS:
1. ***Risk of hepatitis B virus reactivation in patients co-infected with HCV and HBV:***
Hepatitis B virus (HBV) reactivation has been reported in HCV/HBV coinfected patients who were undergoing or had completed treatment with HCV direct acting antivirals, and who were not receiving HBV antiviral therapy. Patients with serologic evidence of HBV infection, monitor for clinical and laboratory signs of hepatitis flare or HBV reactivation during HCV treatment with ABRIVA PLUS and during post -treatment follow-up. Initiate appropriate patient management for HBV infection as clinically indicated.
2. ***Serious symptomatic bradycardia when co-administered with amiodarone:***
Patients also taking beta blockers, or those with underlying cardiac comorbidities and/or advanced liver disease may be at increased risk for symptomatic bradycardia with co-administration of amiodarone. Bradycardia generally resolved after discontinuation of HCV treatment. The mechanism for this effect is unknown. Co-administration of amiodarone with **ABRIVA PLUS** is not recommended. For patients taking amiodarone who have no other alternative viable treatment options and who will be co administered. Counsel patients about the risk of symptomatic bradycardia. Cardiac monitoring in an in-patient setting for the first 48 hours of co administration is recommended, after which outpatient or self-monitoring of the heart rate should occur on a daily basis through at least the first 2 weeks of treatment. Patients who are taking ABRIVA PLUS who need to start amiodarone therapy due to no other alternative viable treatment options should undergo similar cardiac monitoring as outlined above. Patients who develop signs or symptoms of bradycardia should seek medical evaluation immediately. Symptoms may include near-fainting or fainting, dizziness or lightheadedness, malaise, weakness, excessive tiredness, shortness of breath, chest pains, confusion, or memory problems.
3. ***Risk of reduced therapeutic effect due to concomitant use with inducers of P-gp and/or moderate to potent inducers of cyp :***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 significantly decrease plasma concentrations of sofosbuvir and/or velpatasvir, leading to potentially reduced therapeutic effect. The use of these agents is not recommended.
4. ***Risks associated with ribavirin combination treatment:***
If administered with ribavirin, the warnings and precautions for ribavirin apply to this combination regimen. Refer to the ribavirin prescribing information for a full list of the warnings and precautions for ribavirin.

DRUG INTERACTIONS:
Potential for other drugs to affect: 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 effects. The use of these agents is not recommended. Sofosbuvir/ Velpatasvir may be co- administered with P-gp, BCRP, and CYP inhibitors.
Potential to affect other drugs: Velpatasvir is an inhibitor of drug transporters P-gp, breast cancer resistance Protein (BCRP), OATP1B1, OATP1B3, and OATP2B1. Co-administration with drugs that are substrates of these transporters may increase the exposure of such drugs.

Back

Potentially significant drug interactions:

Concomitant Drug Class: **Drug Name**	**Effect on Concentration** [b]	**Clinical Effect/Recommendation**
Acid Reducing Agents: Antacids (e.g., aluminum and magnesium hydroxide)	↓velpatasvir	Velpatasvir solubility decreases as pH increases. Drugs that increase gastric pH are expected to decrease concentration of velpatasvir. Separate antacid and ABRIVEL administration by 4 hours.
H_2-receptor antagonists [c] (e.g., famotidine)		H_2-receptor antagonists may be administered simultaneously with or 12 hours apart from ABRIVA PLUS at a dose that does not exceed doses comparable to famotidine 40 mg twice daily.
Proton-pump inhibitors [c] (e.g., omeprazole)		Famotidine 40 mg twice daily. Co-administration of omeprazole or other proton-pump inhibitors is not recommended. If it is considered medically necessary to co administer, It should be administered with food and taken 4 hours before omeprazole 20 mg. Use with other proton-pump inhibitors has not been studied.
Antiarrhythmics: amiodarone	Effect on amiodarone, sofosbuvir, and velpatasvir concentrations unknown	Co-administration of amiodarone with a sofosbuvir- containing regimen may result in serious symptomatic bradycardia. The mechanism of this effect is unknown. Co-administration of amiodarone with ABRIVEL is not recommended; if co-administration is required, cardiac monitoring is recommended.
digoxin [c]	↑digoxin	Therapeutic concentration monitoring of digoxin is recommended when co-administered. Refer to digoxin prescribing information for monitoring and dose modification recommendations for concentration increases of less than 50%.
Anticancers: topotecan	↑topotecan	Co-administration is not recommended.
Anticonvulsants: carbamazepine phenytoin phenobarbital oxcarbazepine	↓sofosbuvir ↓velpatasvir	Co-administration is not recommended.
Antimycobacterials: rifabutin rifampin [c] rifapentine	↓sofosbuvir ↓velpatasvir	Co-administration is not recommended.
HIV Antiretrovirals: efavirenz [c] Regimens containing tenofovir DF	↓velpatasvir ↑	Co-administration of sofos/velpa with efavirenz-containing regimens is not recommended. Monitor for tenofovir-associated adverse reactions in patients using the combination 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	↓sofosbuvir ↓velpatasvir	Co-administration is not recommended.

DF =disoproxil fumarate.
a. This table is not all inclusive.
b. ↓ = decrease, ↑ =increase.
c. Interactions in healthy adults.

USE IN SPECIFIC POPULATIONS:

Pregnancy:
If it is administered with ribavirin, the combination regimen is contraindicated in pregnant women and in men whose female partners are pregnant. Refer to the ribavirin prescribing information for more information on ribavirin-associated risks of use during pregnancy. The background risk of major birth defects and miscarriage for the indicated population is unknown.

Nursing mothers:
It is not known whether the components and its metabolites are present in human breast milk, affect human milk production, or have effects on the breastfed infant.
If it is administered with ribavirin, refer to the ribavirin prescribing information for more information on use during lactation.

Females and males of reproductive potential:
If administered with ribavirin, the information for ribavirin with regard to pregnancy testing, contraception, and infertility also applies to this combination regimen. Refer to ribavirin prescribing information for additional information.

Pediatric use:
Safety and effectiveness of have not been established in pediatric patients.

Geriatric use:
No overall differences in safety or effectiveness between these subjects and younger subjects, but greater sensitivity of some older individuals cannot be ruled out. No dosage adjustment of **ABRIVA PLUS** is warranted in geriatric patients.

Patients with renal impairment:
No dosage adjustment of **ABRIVA PLUS** is required for patients with mild or moderate renal impairment. No dosage recommendation can be given for patients with severe renal impairment or ESRD. Refer to ribavirin prescribing information regarding use of ribavirin in patients with renal impairment.

Patients with hepatic impairment:
No dosage adjustment of **ABRIVA PLUS** is required for patients with mild, moderate, or severe hepatic impairment (Child-Pugh Class A, B, or C). Clinical and hepatic laboratory monitoring (including direct bilirubin), as clinically indicated, is recommended for patients with decompensated cirrhosis receiving treatment with **ABRIVA PLUS** and ribavirin.

ADVERSE REACTIONS:
If administered with ribavirin, refer to the prescribing information for ribavirin for a description of ribavirin-associated adverse reactions.

The following serious adverse reactions are described below and elsewhere in labeling:

- Serious Symptomatic Bradycardia When Co-administered with Amiodarone.
- ***Adverse Reactions in Subjects without Cirrhosis or with Compensated Cirrhosis:***

The most common adverse reactions occurring with mild severity (Grade 1) are headache and fatigue. Adverse reactions greater than or equal t0 5% include headache, fatigue, nausea, asthenia and insomnia.

- ***Adverse Reactions in Subjects Co-infected with HCV and HIV-1:***

The safety profile in HCV/HIV-1 co-infected subjects is similar to that in HCV mono-infected subjects. The most common adverse reactions occurring in at least 10% of subjects were fatigue and headache.

- ***Adverse Reactions in Subjects with Decompensated Cirrhosis:***

The most common adverse reactions are fatigue, anemia, nausea, headache, insomnia and diarrhea. Adverse reactions, 98% are of mild to moderate severity.

- ***Less Common Adverse Reactions:***

Rash at 2% (mild/moderate severity) and Depression at 1% (mild/moderate in severity).

- ***Laboratory Abnormalities:***

Raised levels of Lipase, Creatine Kinase Indirect Bilirubin may occur.

OVERDOSAGE:
No specific antidote is available for overdose. If overdose occurs the patient must be monitored for evidence of toxicity. Treatment of overdose consists of general supportive measures including monitoring of vital signs as well as observation of the clinical status of the patient.

INSTRUCTIONS:
- Store below 30ºC.
- Protect from heat, sunlight & moisture.
- Keep out of the reach of children.
- To be sold on the prescription of a registered medical practitioner only.

PRESENTATION:
ABRIVA PLUS Tablet : Pack of 4 x 7 tablets.

ہدایات:
۳۰ درجہ سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔
گرمی، دھوپ اور نمی سے بچائیں۔
بچوں کی پہنچ سے دور رکھیں۔
صرف ڈاکٹر کے نسخہ پر فروخت کریں۔

FOR FURTHER INFORMATION PLEASE CONTACT:

CCL
Manufactured by:
CCL Pharmaceuticals (Pvt.) Ltd.
62 Industrial Estate, Kot Lakhpat, Lahore, Pakistan.

2708-B
25150-0027-002-0000-0000