Darvoni

Sofosbuvir INN 400 mg + Daclatasvir INN 60 mg Tablet

- Effective treatment regimen for Hepatitis C
- Affordable treatment regimen
- First truly pan-genotypic anti-hep C combination
- Shows superior on-treatment response[2]
- Recommended by the AASLD & EASL and USFDA approved[1,2]

Prescribing Information

COMPOSITION: Darvoni Tablet: Each film coated tablet contains Sofosbuvir INN 400 mg and Daclatasvir Dihydrochloride INN equivalent to Daclatasvir 60 mg. **PHARMACOLOGICAL INFORMATION** Therapeutic class: Antiviral agent **PHARMACOLOGICAL ACTION** Mechanism of Action Sofosbuvir directly targets the Hepatitis C virus to stop it from making copies of itself in the liver. Sofosbuvir attaches itself to the genetic information, called RNA, to block the virus from multiplying. And Daclatasvir is a Direct-acting Antiviral Agent (DAA) against the hepatitis C virus. **CLINICAL INFORMATION** Therapeutic Indications Sofosbuvir and Daclatasvir combination indicated for the treatment of chronic hepatitis C (CHC) infection as a component of a combination antiviral treatment regimen. Treatment regimen and duration are dependent on both viral genotype and patient population. Treatment response varies based on baseline host and viral factors. Dosage Recommended Dose in Adults The recommended dose of Sofosbuvir is one 400 mg and Daclatasvir 60 mg tablet, taken orally, once daily with or without food. Sofosbuvir and Daclatasvir combination should be used in combination with or without ribavirin for the treatment of CHC in adults. Dosage Modification Due to Drug Interactions: Refer to the drug interactions and contraindication sections for other drugs before co-administration with Sofosbuvir and Daclatasvir combination Strong inhibitors of Cytochrome P450 enzyme 3A (CYP3A): Reduce the dosage of Daclatasvir to 30 mg once daily when co-administered with strong CYP3A inhibitors using the 30 mg tablet. Moderate CYP3A inducers: Increase the dosage of Daclatasvir to 90 mg once daily using an appropriate combination of tablets (three 30 mg tablets or one 60 mg and one 30 mg. tablet) when co-administered with moderate CYP3A inducers. Strong CYP3A inducers: Daclatasvir is contraindicated in combination with strong CYP3A inducers. Dose Modification Dosage reduction of Sofosbuvir and Daclatasvir combination for adverse reactions is not recommended Discontinuation of Dosing If the other agents used in combination with Sofosbuvir and Daclatasvir combination are permanently discontinued, Sofosbuvir and Daclatasvir combination should also be discontinued. Severe Renal Impairment and End Stage Renal Disease No dose recommendation can be given for patients with severe renal impairment (estimated Glomerular Filtration Rate (eGFR) <30 mL/min/1.73m2) or with End Stage Renal Disease (ESRD) **Side Effects** The most common adverse events observed with Sofosbuvir and Daclatasvir in combination with Ribavirin were fatigue and headache. There are some rare side effects, such as Fatigue, Headache, Insomnia, Nausea, Pruritus, Anemia, Asthenia, Rash, Anorexia, Chills, Infulenza Like Illness, **Contraindications** When Sofosbuvir and Daclatasvir is used in combination with Ribavirin, the contraindications applicable to those agents are applicable to combination therapies. Ribavirin for a list of their contraindications. Sofosbuvir and Daclatasvir combination treatment with Ribavirin is contraindicated in women who are pregnant or may become pregnant and men whose female partners are pregnant because of the risks for birth defects and fetal death associated with Ribavirin. Drug interactions Drugs that are potent intestinal P-gp inducers (e.g., Rifampin, St. John's wort) may alter the concentrations of Sofosbuvir. Consult the full prescribing information prior to use for potential drug-drug interactions. Potential for Other Drugs to Affect Daclatasvir: Daclatasvir is a substrate of CYP3A. Therefore, moderate or strong inducers of CYP3A may decrease the plasma levels and therapeutic effect of Daclatasvir. Strong inhibitors of CYP3A (e.g., Clarithromycin, Itraconazole, Ketoconazole, Ritonavir) may increase the plasma levels of Daclatasvir. Potential for Daclatasvir to Affect Other Drugs: Daclatasvir is an inhibitor of P-glycoprotein transporter (P-gp), organic anion transporting polypeptide (OATP) 1B1 and 1B3 and Breast Cancer Resistance Protein (BCRP). Administration of Daclatasvir may increase systemic exposure to medicinal products thatare substrates of P-gp, OATP 1B1 or 1B3 or BCRP, which could increase or prolong theirtherapeutic effect or adverse reactions. Established and Potentially Significant Drug Interactions: Refer to the prescribing information for Sofosbuvir for drug interaction information. The most conservative recommendation should be followed. **Precautions** Pregnancy: If Ribavirin is used with this combination it may cause birth defects and fetal death and animal studies have shown interferons have abortifacient effects; avoid pregnancy in female patients and female partners of male patients. Patients must have a negative pregnancy test prior to initiating therapy, use at least 2 effective non-hormonal methods of contraception and have monthly pregnancy tests Pregnancy Pregnancy Category B Daclatasvir: No data with Daclatasvir in pregnant women are available to inform a drug-associated risk. In animal reproduction studies in rats and rabbits, no evidence of fetal harm was observed with oral administration of Daclatasvir during organogenesis at doses that produced exposures up to 6 and 22 times, respectively, the recommended human dose (RHD) of 60 mg. However, embryofetal toxicity was observed in rats and rabbits at maternally toxic doses that produced exposures of 33 and 98 times the human exposure, respectively, at the RHD of 60 mg. consider the benefits and risks of Daclatasvir when prescribing Daclatasvir to a pregnant woman Nursing Mothers It is not known whether Sofosbuvir and its metabolites are present in human breast milk. The predominant circulating metabolite GS-331007 was the primary component observed in the milk of lactating rats, without effect on nursing pups. Because of the potential for adverse reactions from the drug in nursing infants, a decision must be made whether to discontinue nursing or discontinue treatment with Ribavirin-containing regimens, taking into account the importance of the therapy to the mother. No information regarding the presence of Daclatasvir in human milk, the effects on the breastfed infant or the effects on milk production is available. Daclatasvir is present in the milk of lactating rats. The development and health benefits of breastfeeding should be considered along with the mother's clinical need for Daclatasvir and any potential adverse effects on the breastfed infant from Daclatasvir or from the underlying maternal condition. **Pediatric Use** Safety and effectiveness of Sofosbuvir in children less than 18 years of age have not been established. Safety and effectiveness of Daclatasvir in children less than 18 years of age have not been established. **Geriatric Use** Sofosbuvir was administered to 90 subjects aged 65 and over. The response rates observed for subjects over 65 years of age were similar to that of younger subjects across treatment groups. No dose adjustment of Sofosbuvir is warranted in geriatric patients. Safety was similar across older and younger subjects and there were no safety findings unique to subjects 65 years and older. Sustained virologic response (SVR) rates were comparable among older and younger subjects. No dosage adjustment of Daclatasvir is required for elderly patients. Patients with Impaired Renal Function No dose adjustment of Sofosbuvir is required for patients with mild or moderate renal impairment. The safety and efficacy of Sofosbuvir have not been established in patients with severe renal impairment (eGFR<30 mL/min/1.73m2) or End Stage Renal Disease (ESRD) requiring hemodialysis. No dose recommendation can be given for patients with severe renal impairment or ESRD. Refer also to Ribavirin and Peginterferon alfa prescribing information for patients with CrCl<50 mL/min. No dosage adjustment of Daclatasvir is required for patients with any degree of renal impairment. Hepatic Impairment No dose adjustment of Sofosbuvir is required for patients with mild, moderate or severe hepatic impairment (Child-Pugh Class A, B or C). Safety and efficacy of Sofosbuvir have not been established in patients with decompensated cirrhosis. No dosage adjustment of Daclatasvir is required for patients with mild (Child-Pugh A), moderate (Child-Pugh B), or severe (Child-Pugh C) hepatic impairment. Safety and efficacy of Daclatasvir have not been established in patients with decompensated cirrhosis. **Overdosage** The highest documented dose of Sofosbuvir was a single supratherapeutic dose of Sofosbuvir 1200 mg administered to 59 healthy subjects. In that trial, there were no untoward effects observed at this dose level, and adverse events were similar in frequency and severity to those reported in the placebo and Sofosbuvir 400 mg treatment groups. The effects of higher doses are not known. No specific antidote is available for overdose with Sofosbuvir. If overdose occurs the patient must be monitored for evidence of toxicity. Treatment of overdose with Sofosbuvir consists of general supportive measures including monitoring of vital signs as well as observation of the clinical status of the patient. A 4-hour hemodialysis session removed 18% of the administered dose. There is no known antidote for overdose of Daclatasvir. Treatment of overdose with Daclatasvir should consist of general supportive measures, including monitoring of vital signs and observation of the patient's clinical status. Because Daclatasvir is highly protein bound (>99%), dialysis is unlikely to significantly reduce plasma concentrations of the drug. **PHARMACEUTICAL INFORMATION** Storage Conditions Store in a cool and dry place, away from light. Keep out of the reach of children. **Packaging & Presentation** Darvoni Tablet: Each commercial box contains 1 X 6's tablets in Alu-Alu blister pack.

BEACON Pharmaceuticals Limited

Light for life

Darvoni

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True **Pan-genotypic** combination in the fight against Hepatitis C

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Both treatment naïve and experienced patient has shown up to **100%** virological response rate in the treatment with Sofosbuvir and Daclatasvir.

Parameter On-treatment response, n(%)	Treatment Naive (N=101)	Treatment Experienced (N=51)
Week 1 HCV RNA <LL0Q, detectable or undetectable	40 (40)	12 (24)
Week 1 HCV RNA <LL0Q, detectable or undetectable	78 (77)	35 (69)
Week 4 HCV RNA <LL0Q, detectable or undetectable HCV RNA undetectable	95 (94) 64 (63)	50 (98) 37 (73)
End of treatment HCV RNA <LL0Q, detectable or undetectable HCV RNA undetectable	100 (99) 100 (99)	51 (100) 51 (100)

Ref: Hepatology. 2015 Apr;61(4):1127-35

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Hepatitis C treatment guideline by the EASL[2]

Daclatasvir & Sofosbuvir

	G-1a	G-1b	G-2	G-3	G-4	G-5 and G-6
Treatment naïve and PI failed patients (No Cirrhosis)	12 W Without *RBV	12 W Without RBV	12 W Without RBV	**12 W Without RBV**	12 W Without RBV	12 W Without RBV
Treatment naïve and PI failed patients (compensated Cirrhosis)	12 W with RBV, or 24 W without RBV		12 W Without RBV	**24 W With RBV**	12 W with RBV, or 24 W without RBV	12 W with RBV, or 24 W without RBV
Patients with decompensated cirrhosis (Child-Pugh B and Child-Pugh C, up to 12 points)	12 W With RBV					
Patients with decompensated cirrhosis (Child-Pugh B and Child-Pugh C, up to 12 points) When Ribavirin is contraindicated	24 W without RBV					

*RBV = Ribavirin

Ref: EASL Recommendations on Treatment of Hepatitis C 2015