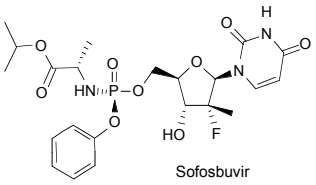
Cuverol™

[Sofosbuvir]

400mg Tablets

DESCRIPTION

Cuverol (Sofosbuvir) is a nucleotide inhibitor of HCV NS5B RNA-dependant RNA polymerase. Chemically, sofosbuvir is (S)-Isopropyl 2-((S)-(((2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl)methoxy)-(phenoxy)phosphorylamino)propanoate. Its molecular formula is $C_{22}H_{29}FN_3O_9P$ and the structural formula is:



Sofosbuvir

QUALITATIVE & QUANTITATIVE COMPOSITION

Cuverol (Sofosbuvir) is available for oral administration as:

Cuverol Tablets 400mg
Each film-coated tablet contains:
Sofosbuvir... 400mg

CLINICAL PHARMACOLOGY

Mechanism of Action

Sofosbuvir is a direct-acting antiviral agent against the hepatitis C virus. It is a pan-genotypic inhibitor of the HCV NS5B RNA-dependent RNA polymerase, which is essential 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.

Pharmacokinetics

Absorption

Following oral administration sofosbuvir was absorbed with a peak plasma concentration observed at ~0.5-2 hour post-dose, regardless of dose level. Peak plasma concentration of GS-331007 was observed between 2 to 4 hours post-dose.

Effect of Food

Relative to fasting conditions, the administration of a single dose of sofosbuvir with a standardised high fat meal slowed the rate of absorption of sofosbuvir. The extent of absorption of sofosbuvir was increased approximately 1.8-fold but it did not substantially affect the sofosbuvir C_{max} or AUC_{0-inf}. The exposure of GS-331007 was not altered in the presence of a high-fat meal. Therefore, sofosbuvir can be administered without regard to food.

Distribution

Sofosbuvir is approximately 61-65% bound to human plasma proteins and the binding is independent of drug concentration over the range of 1µg/mL to 20µg/mL. Protein binding of GS-331007 was minimal in human plasma. After a single 400mg dose of [^{14}C]-sofosbuvir in healthy individuals, the blood to plasma ratio of ^{14}C-radioactivity was approximately 0.7.

Metabolism

Sofosbuvir is extensively metabolized in the liver to form the pharmacologically active nucleoside analog triphosphate GS-461203. The metabolic activation pathway involves sequential hydrolysis of the carboxyl ester moiety catalyzed by human cathepsin A (CatA) or carboxylesterase 1 (CES1) and phosphoramidate cleavage by histidine triad nucleotide-binding protein 1 (HINT1) followed by phosphorylation by the pyrimidine nucleotide biosynthesis pathway. Dephosphorylation results in the formation of nucleoside metabolite GS-331007 that cannot be efficiently rephosphorylated and lacks anti-HCV activity *in vitro*.

Elimination

Following a single 400mg oral dose of [^{14}C]-sofosbuvir, mean total recovery of the dose was greater than 92%, consisting of approximately 80%, 14%, and 2.5% recovered in urine, feces, and expired air, respectively. The majority of the sofosbuvir dose recovered in urine was GS-331007 (78%) while 3.5% was recovered as sofosbuvir. The median terminal half-lives of sofosbuvir and GS-331007 were 0.4 and 27 hours, respectively.

Special Populations

Renal impairment

The pharmacokinetics of sofosbuvir were studied in HCV negative patients. Relative to subjects with normal renal function, the sofosbuvir AUC_{0-inf} was 61%, 107% and 171% higher in mild, moderate and severe renal impairment. Sofosbuvir AUC_{0-inf} was 28% higher when sofosbuvir was dosed 1 hour before hemodialysis compared with 60% higher when sofosbuvir was dosed 1 hour after hemodialysis.

Hepatic impairment

The pharmacokinetics of sofosbuvir were studied in HCV-infected patients. Relative to subjects with normal hepatic function, the sofosbuvir AUC_{0-24} were 126% and 143% higher in moderate and severe hepatic impairment.

THERAPEUTIC INDICATIONS

Cuverol (Sofosbuvir) is indicated for the treatment of chronic hepatitis C (CHC) infection as a component of a combination antiviral treatment regimen in adults.

DOSAGE & ADMINISTRATION

The recommended dose of Cuverol (Sofosbuvir) is one 400mg tablet, taken orally, once daily with or without food.

Cuverol (Sofosbuvir) should be used in combination with ribavirin or in combination with peginterferon and ribavirin for the treatment of CHC in adults. The recommended regimen and treatment duration for Cuverol (Sofosbuvir) combination therapy is provided in table below:

Recommended Regimens and Treatment Duration for Cuverol (Sofosbuvir) Combination Therapy in HCV Mono-infected and HCV/HIV-1 Coinfected Patients

Patients	Treatment	Duration
Patients with genotype 1, 4, 5 or 6 CHC	Cuverol + ribavirin + peginterferon alfa	12 weeks[a,b]
	Cuverol + ribavirin Only for use in patients ineligible or intolerant to peginterferon alfa	24 weeks
Patients with genotype 2 CHC	Cuverol + ribavirin	12 weeks[b]
Patients with genotype 3 CHC	Cuverol + ribavirin + peginterferon alfa	12 weeks[b]
	Cuverol + ribavirin	24 weeks
Patients with CHC awaiting liver transplantation	Cuverol + ribavirin	48 weeks or Until liver transplantation

a. For previously treated patients with HCV genotype 1 infection, no data exists with the combination of Cuverol, ribavirin and peginterferon alfa.
b. Consideration should be given to potentially extending the duration of therapy beyond 12 weeks and up to 24 weeks; especially for those subgroups who have one or more factors historically associated with lower response rates to interferon-based therapies (e.g. advanced fibrosis/cirrhosis, high baseline viral concentrations, black race, IL28B non CC genotype, prior null response to peginterferon alfa and ribavirin therapy).

The dose of ribavirin, when used in combination with Cuverol (Sofosbuvir) is weight-based (<75 kg = 1000mg and ≥75 kg = 1200mg) and administered orally in two divided doses with food.

Dose modification

Dose reduction of Cuverol (Sofosbuvir) is not recommended.

Genotype 1, 4, 5 and 6

If a patient has a serious adverse reaction potentially related to peginterferon alfa and/or ribavirin, the peginterferon alfa and/or ribavirin dose should be reduced or discontinued.

Genotype 2 and 3

If a patient has a serious adverse reaction potentially related to ribavirin, the ribavirin dose should be modified or discontinued, if appropriate, until

the adverse reaction abates or decreases in severity. Table below provides guidelines for dose modifications and discontinuation based on the patient's hemoglobin concentration and cardiac status.

Ribavirin dose modification guideline for co-administration with Cuverol (Sofosbuvir)

Laboratory values	Reduce ribavirin dose to 600 mg/day if:	Discontinue ribavirin if:
Hemoglobin in patients with no cardiac disease	<10 g/dL	<8.5 g/dL
Hemoglobin in patients with history of stable cardiac disease period	≥ 2 g/dL decrease in hemoglobin during any 4 week treatment	<12 g/dL despite 4 weeks at reduced dose

Once ribavirin has been withheld due to either a laboratory abnormality or clinical manifestation, an attempt may be made to restart ribavirin at 600mg daily and further increase the dose to 800mg daily. However, it is not recommended that ribavirin be increased to the original assigned dose (1000mg to 1200mg daily).

Discontinuation of Dosing
If the other medicinal products used in combination with Cuverol (Sofosbuvir) are permanently discontinued, Cuverol (Sofosbuvir) should also be discontinued.

Special Population
Elderly
No dose adjustment is required for elderly patients.

Pediatric population
Cuverol (Sofosbuvir) is not recommended for use in children and adolescents under 18 years of age because the safety and efficacy have not been established in this population.

Renal impairment
No dose adjustment of Cuverol (Sofosbuvir) is required for patients with mild or moderate renal impairment. The safety of sofosbuvir has not been assessed in patients with severe renal impairment or ESRD.

Hepatic impairment
No dose adjustment of Cuverol (Sofosbuvir) is required for patients with mild, moderate or severe hepatic impairment.

ADVERSE REACTIONS
The following adverse reactions have been reported during treatment with sofosbuvir:

Sofosbuvir + Ribavirin
Very common:
Hemoglobin decreased, insomnia, headache, nausea, blood bilirubin increased, fatigue and irritability.

Common:
Nasopharyngitis, anemia, depression, disturbance in attention, dyspnea, dyspnea exertional, cough, abdominal discomfort, constipation, dyspepsia, alopecia, dry skin, pruritus, arthralgia, back pain, musde spasms, myalgia pyrexia and asthenia.

Sofosbuvir + Ribavirin + Peginterferon alfa
Very common:
Anemia, neutropenia, lymphocyte count decreased, platelet count decreased, decreased appetite, insomnia, dizziness, headache, dyspnea, cough, diarrhea, nausea, vomiting, blood bilirubin increased, rash, pruritus, arthralgia, myalgia, chills, fatigue, influenza-like illness, irritability, pain and pyrexia.

Common:
Weight decreased, depression, anxiety, agitation, migraine, memory impairment, disturbance in attention, vision blurred, dyspnea exertional, constipation, dry mouth, gastroesophageal reflux, alopecia, dry skin, back pain, muscle spasms, chest pain and asthenia.

CONTRAINDICATIONS
- Sofosbuvir is contraindicated in patients with known hypersensitivity to sofosbuvir or to any excipient of the product.
- When sofosbuvir is used in combination with ribavirin or peginterferon alfa/ribavirin, the contraindications applicable to those agents are applicable to combination therapies.

PRECAUTIONS
General
Sofosbuvir is not recommended for administration as monotherapy and should be prescribed in combination with other medicinal products for the treatment of hepatitis C infection.

Co-administration with other direct-acting antivirals against HCV
Sofosbuvir should only be co-administered with other direct-acting antiviral medicinal products if the benefit is considered to outweigh the risks based upon available data.

Effect on ability to drive and use machine
Sofosbuvir has moderate influence on the ability to drive and use machine. Patients should be cautioned about the risk of an influence on their ability to drive a car and operate machinery.

Pregnancy
When sofosbuvir is used in combination with ribavirin or peginterferon alfa/ribavirin, extreme caution must be taken to 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 methods of contraception and have monthly pregnancy tests.

Nursing Mothers
It is unknown whether sofosbuvir and its metabolites are excreted in human milk. Because of the potential for adverse reactions from the drug in nursing infants, sofosbuvir should not be used during breast-feeding.

DRUG INTERACTIONS
P-gp inducers
Drugs that are potent P-gp inducers in the intestine (e.g., rifampin or St. John's wort) may decrease sofosbuvir plasma concentration leading to reduced therapeutic effect of sofosbuvir and thus should not be used with sofosbuvir.

Antiarrhythmics
Co-administration of amiodarone with sofosbuvir in combination with another direct acting antiviral is not recommended; as such combination may result in serious symptomatic bradycardia. If co-administration is required, cardiac monitoring is recommended.

Anticonvulsants
Co-administration of sofosbuvir with carbamazepine, phenytoin, phenobarbital or oxcarbazepine is expected to decrease the concentration of sofosbuvir, leading to reduced therapeutic effect of sofosbuvir. Such co-administration is not recommended.

Antimycobacterials
Co-administration of sofosbuvir with rifabutin or rifapentine is expected to decrease the concentration of sofosbuvir, leading to reduced therapeutic effect of sofosbuvir. Such co-administration is not recommended. Sofosbuvir should not be used with rifampin.

HIV Protease Inhibitors
Co-administration of sofosbuvir with tipranavir/ritonavir is expected to decrease the concentration of sofosbuvir, leading to reduced therapeutic effect of sofosbuvir. Such co-administration is not recommended.

Analeptics
Co-administration of sofosbuvir with modafinil is expected to decrease the concentration of sofosbuvir, leading to reduced therapeutic effect of sofosbuvir. Such co-administration is not recommended.

OVERDOSAGE
The highest documented dose of sofosbuvir was a single supratherapeutic dose of sofosbuvir 1200mg, there were no untoward effects observed at this dose level.
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.

STORAGE
Store below 30°C.
Protect from sunlight and moisture.

The expiration date refers to the product correctly stored at the required conditions.

HOW SUPPLIED
Cuverol (Sofosbuvir) Tablets 400mg are available in a bottle of 28's.

Keep out of reach of children.

To be sold on prescription of a registered medical practitioner only.

Please read the contents carefully before use.
This package insert is continually updated from time to time.

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