OCVIR™ 400mg Tablets
(Sofosbuvir)

DESCRIPTION:
OCVIR™ (sofosbuvir) tablets are for oral administration. **OCVIR™** is a nucleotide analog inhibitor of HCV NS5B polymerase. It has a molecular formula of $C_{22}H_{29}FN_3O_9P$

COMPOSITION:
OCVIR™ 400mg tablets
Each film coated tablet contains:
Sofosbuvir MS.....400mg

CLINICAL PHARMACOLOGY:
Mechanism of action
Sofosbuvir is a direct-acting antiviral agent against the hepatitis C virus

Sofosbuvir is an 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. In a biochemical assay, GS-461203 inhibited the polymerase activity of the recombinant NS5B from HCV genotype 1b, 2a, 3a and 4a with IC_{50} values ranging from 0.7 to 2.6 micromolar. GS-461203 is neither an inhibitor of human DNA and RNA polymerases nor an inhibitor of mitochondrial RNA polymerase

Pharmacodynamics
Cardiac Electrophysiology: The effect of sofosbuvir 400 and 1200mg (three times the recommended dosage) on QTc interval was evaluated in a randomized, single-dose, placebo - and active - controlled (moxifloxacin 400mg) four period crossover thorough QT trial in 59 healthy subjects. At a dosage three times the maximum recommended dosage, sofosbuvir does not prolong QTc to any clinically relevant extent

Pharmacokinetics
Absorption: The pharmacokinetic properties of sofosbuvir and the predominant circulating metabolite GS-331007 have been evaluated in healthy adult subjects and in subjects with chronic hepatitis C. Following oral administration of sofosbuvir, sofosbuvir was absorbed with a peak plasma concentration observed at ~ 0.5 to 2 hours 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 standardized high fat meal did not substantially affect the sofosbuvir C_{max} or $AUC_{0\text{-}inf}$. 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 1 microgram/mL to 20 microgram/mL. Protein binding of GS-331007 was minimal in human plasma. After a single 400mg dose of [^{14}C]-sofosbuvir in healthy subjects, 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

After a single 400mg oral dose of [^{14}C]-sofosbuvir, sofosbuvir and GS-331007 accounted for approximately 4% and greater than 90% of drug related material (sum of molecular weight-adjusted AUC of sofosbuvir and its metabolites) systemic exposure, respectively

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. These data indicate that renal clearance is the major elimination pathway for GS-331007. The median terminal half-lives of sofosbuvir and GS-331007 were 0.4 and 27 hours, respectively

Assessment of Drug Interactions: Sofosbuvir is a substrate of drug transporter P-gp and breast cancer resistance protein (BCRP) while GS-331007 is not. Drugs that are 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 concomitant use with sofosbuvir is not recommended

Coadministration of sofosbuvir with drugs that inhibit P-gp and/or BCRP may increase sofosbuvir plasma concentration without increasing GS-331007 plasma concentration; accordingly, sofosbuvir may be coadministered with P-gp and / or BCRP inhibitors. Sofosbuvir and GS-331007 are not inhibitors of P-gp and BCRP and thus are not expected to increase exposures of drugs that are substrates of these transporters

The intracellular metabolic activation pathway of sofosbuvir is mediated by generally low affinity and high capacity hydrolase and nucleotide phosphorylation pathways that are unlikely to be affected by concomitant drugs

The effects of coadministered drugs on the exposure of sofosbuvir and GS-331007 are shown in table below:

Drug Interactions: Changes in Pharmacokinetic Parameters for Sofosbuvir and the Predominant Circulating Metabolite GS-331007 in the Presence of the Coadministered Drug[a]

Co-administered Drug	Dose of Co-administered Drug (mg)	Sofosbuvir Dose (mg)	N	Mean Ratio (90% CI) of Sofosbuvir and GS-331007 PK with/without Co-administered Drug No Effect = 1.00			
					C_{max}	AUC	C_{min}
Cyclosporine	600 single dose	400 single dose	19	sofosbuvir	2.54 (1.87, 3.45)	4.53 (3.26, 6.30)	NA
				GS-331007	0.60 (0.53, 0.69)	1.04 (0.90, 1.20)	NA
Darunavir (boosted with ritonavir)	800/100 once daily	400 single dose	18	sofosbuvir	1.45 (1.10, 1.92)	1.34 (1.12, 1.59)	NA
				GS-331007	0.97 (0.90, 1.05)	1.24 (1.18, 1.30)	NA
Efavirenz[c]	600 once daily	400 single dose	16	sofosbuvir	0.81 (0.60, 1.10)	0.94 (0.76, 1.16)	NA
Emtricitabine[c]	200 once daily						
Tenofovir disoproxil fumarate[c]	300 once daily			GS-331007	0.77 (0.70, 0.84)	0.84 (0.76, 0.92)	NA
Methadone	30 to 130 once daily	400 once daily	14	sofosbuvir	0.95[b] (0.68, 1.33)	1.30[b] (1.00, 1.69)	NA
				GS-331007	0.73[b] (0.65, 0.83)	1.04[b] (0.89, 1.22)	NA
Rilpivirine	25 once daily	400 single dose	17	sofosbuvir	1.21 (0.90, 1.62)	1.09 (0.94, 1.27)	NA
				GS-331007	1.06 (0.99, 1.14)	1.01 (0.97, 1.04)	NA
Tacrolimus	5 single dose	400 single dose	16	sofosbuvir	0.97 (0.65, 1.43)	1.13 (0.81, 1.57)	NA
				GS-331007	0.97 (0.83, 1.14)	1.00 (0.87, 1.13)	NA

NA = not available / not applicable
a) All interaction studies conducted in healthy volunteers
b) Comparison based on historic control
c) Administered as efavirenz / emtricitabine / tenofovir disoproxil fumarate fixed dose tablet
No effect on the pharmacokinetic parameters of sofosbuvir and GS-331007 was observed with reltegravir

210 mm

150 mm

Drug Interactions: Changes in Pharmacokinetic Parameters for co-administered drug in the presense of Sofosbuvir[a]

Co-administered Drug	Dose of Co-administered Drug (mg)	Sofosbuvir Dose (mg)	N	Mean Ratio (90% CI) of Co-administered Drug PK with/without Sofosbuvir No Effect = 1.00		
				C_{max}	AUC	C_{min}
Norelgestromin	norgestimate 0.18 / 0.215 / 0.25 ethinyl estradiol 0.025, once daily	400 once daily	15	1.07 (0.94, 1.22)	1.06 (0.92, 1.21)	1.07 (0.89, 1.28)
Norgestrel				1.18 (0.99, 1.41)	1.19 (0.98, 1.45)	1.23 (1.00, 1.51)
Ethinyl estradiol				1.15 (0.97, 1.36)	1.09 (0.94, 1.26)	0.99 (0.80, 1.23)
Raltegravir	400 twice daily	400 single dose	19	0.57 (0.44, 0.75)	0.73 (0.59, 0.91)	0.95 (0.81, 1.12)
Tacrolimus	5 single dose	400 single dose	16	0.73 (0.59, 0.90)	1.09 (0.84, 1.40)	NA
Tenofovir disoproxil fumarate[b]	300 once daily	400 single dose	16	1.25 (1.08, 1.45)	0.98 (0.91, 1.05)	0.99 (0.91, 1.07)

NA = not available / not applicable
a) All interaction studies conducted in healthy volunteers
b) Administered as efavirenz / emtricitabine / tenofovir disoproxil fumarate fixed dose tablet
No effect on the pharmacokinetic parameters of the following co-administered drugs was observed with sofosbuvir: cyclosporine, darunavir / ritonavir, efavirenz, emtricitabine, methadone, or rilpivirine

Microbiology
Antiviral Activity: In HCV replicon assays, the EC_{50} values of sofosbuvir against full-length replicons from genotype 1a, 1b, 2a, 3a and 4a, and chimeric 1b replicons encoding NS5B from genotype 2b, 5a or 6a ranged from 0.014 to 0.11 micromolar. The median EC_{50} value of sofosbuvir against chimeric replicons encoding NS5B sequences from clinical isolates was 0.062 micromolar for genotype 1a (range 0.029 – 0.128 micromolar; N=67), 0.102 micromolar for genotype 1b (range 0.045 – 0.170 micromolar; N=29), 0.029 micromolar for genotype 2 (range 0.014–0.081 micromolar; N=15) and 0.081 micromolar for genotype 3a (range 0.024 – 0.181 micromolar; N=106). In infectious virus assays, the EC_{50} values of sofosbuvir against genotype 1a and 2a were 0.03 and 0.02 micromolar, respectively. The presence of 40% human serum had no effect on the anti-HCV activity of sofosbuvir. Evaluation of sofosbuvir in combination with interferon alpha or ribavirin showed no antagonistic effect in reducing HCV RNA levels in replicon cells

INDICATIONS AND USAGE:
Sofosbuvir is indicated for the treatment of genotype 1, 2, 3 or 4 chronic hepatitis C virus (HCV) infection as a component of a combination antiviral treatment regimen

DOSAGE AND ADMINISTRATION:
Recommended Dosage
The recommended dosage of sofosbuvir is one 400mg tablet, taken orally, once daily with or without food
Administer sofosbuvir in combination with ribavirin or in combination with pegylated interferon and ribavirin for the treatment of HCV. The recommended treatment regimen and duration for sofosbuvir combination therapy is provided in table below:

For patients with HCV/HIV-1 co-infection, follow the dosage recommendations in table below. Refer to Drug Interactions for dosage recommendations for concomitant HIV-1 antiviral drugs

Recommended Treatment Regimens and Duration

Pateint Population	Treatment Regimen	Duration
Genotype 1 or 4	Sofosbuvir + peginterferon alfa[a] + ribavirin[b]	12 Weeks
Genotype 2	Sofosbuvir + ribavirin[b]	12 Weeks
Genotype 3	Sofosbuvir + ribavirin[b]	24 Weeks
a) See peginterferon alfa prescribing information for dosage recommendation for patients with genotype 1 or 4 HCV b) Dosage of ribavirin is weight-based (<75 kg = 1000mg and ≥75 kg = 1200mg). The daily dosage of ribavirin is administered orally in two divided doses with food. Patients with renal impairment (CrCl ≥ 50mL/min) require ribavirin dosage reduction; refer to ribavirin prescribing information		

Patients with Genotype 1 HCV Who are Ineligible to Receive an Interferon-Based Regimen: Sofosbuvir in combination with ribavirin for 24 weeks can be considered as a therapeutic option for patients with genotype 1 infection who are ineligible to receive an interferon-based regimen. Treatment decision should be guided by an assessment of the potential benefits and risks for the individual patient

Patients with Hepatocellular Carcinoma Awaiting Liver Transplantation: Administer sofosbuvir in combination with ribavirin for up to 48 weeks or until the time of liver transplantation, whichever occurs first, to prevent post-transplant HCV reinfection

Dosage Modification
Dosage reduction of sofosbuvir is not recommended

If a patient has a serious adverse reaction potentially related to peginterferon alfa and/or ribavirin, the peginterferon alfa and/or ribavirin dosage should be reduced or discontinued, if appropriate, until the adverse reaction abates or decreases in severity. Refer to the peginterferon alfa and ribavirin prescribing information for additional information about how to reduce and/or discontinue the peginterferon alfa and/or ribavirin dosage

Discontinuation of Dosing
If the other agents used in combination with sofosbuvir are permanently discontinued, sofosbuvir should also be discontinued

Severe Renal Impairment and End Stage Renal Disease
No dosage recommendation can be given for patients with severe renal impairment (estimated Glomerular Filtration Rate [eGFR] less than 30mL / min / 1.73m^2) or with end stage renal disease (ESRD) due to higher exposures (up to 20-fold) of the predominant sofosbuvir metabolite

CONTRAINDICATIONS:
When sofosbuvir is used in combination with ribavirin or peginterferon alfa / ribavirin, the contraindications applicable to those agents are applicable to combination therapies. Refer to the prescribing information of peginterferon alfa and ribavirin for a list of their contraindications

WARNINGS AND PRECAUTIONS:
Serious Symptomatic Bradycardia When Coadministered with Amiodarone and Another HCV Direct Acting Antiviral
Postmarketing cases of symptomatic bradycardia and cases requiring pacemaker intervention have been reported when amiodarone is coadministered with sofosbuvir in combination with an investigational agent (NS5A inhibitor) or simeprevir. A fatal cardiac arrest was reported in a patient receiving a sofosbuvir-containing regimen (ledipasvir / sofosbuvir). Bradycardia has generally occurred within hours to days, but cases have been observed up to 2 weeks after initiating HCV treatment. 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 coadministration of amiodarone. Bradycardia generally resolved after discontinuation of HCV treatment. The mechanism for this effect is unknown Coadministration of amiodarone with sofosbuvir in combination with another direct acting antiviral (DAA) is not recommended. For patients taking amiodarone who have no other alternative, viable treatment options and who will be coadministered sofosbuvir and another DAA:

- Counsel patients about the risk of serious symptomatic bradycardia
- Cardiac monitoring in an in-patient setting for the first 48 hours of coadministration 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 sofosbuvir in combination with another DAA who need to start amiodarone therapy due to no other alternative, viable treatment options should undergo similar cardiac monitoring as outlined above

Due to amiodarone's long half-life, patients discontinuing amiodarone just prior to starting sofosbuvir in combination with a DAA should also 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

Risk of Reduced Therapeutic Effect Due to Use with P-gp Inducers
Drugs that are P-gp inducers in the intestine (e.g. rifampin, St. John's wort) may significantly decrease sofosbuvir plasma concentrations and may lead to a reduced therapeutic effect of sofosbuvir. The use of rifampin and St. John's wort with sofosbuvir is not recommended

Risks Associated with Combination Treatment
Because sofosbuvir is used in combination with other antiviral drugs for treatment of HCV infection, consult the prescribing information for these drugs used in combination with sofosbuvir. Warnings and precautions related to these drugs also apply to their use in sofosbuvir combination treatment

Related Products Not Recommended
The use of sofosbuvir with other products containing sofosbuvir is not recommended

ADVERSE REACTIONS:
The following serious adverse reactions are described below and elsewhere in the labelling:

- Serious Symptomatic Bradycardia when coadministered with Amiodarone and another HCV Direct Acting Antiviral

Less Common Adverse Reactions Reported in Clinical Trials (less than 1%):
Hematologic Effects: Pancytopenia (particularly in subjects receiving concomitant pegylated interferon)

Psychiatric Disorders: Severe depression (particularly in subjects with pre-existing history of psychiatric illness), including suicidal ideation and suicide

Bilirubin Elevations
Total bilirubin elevation of more than 2.5xULN was observed in none of the subjects in the sofosbuvir + peginterferon alfa + ribavirin 12 weeks group and in 1%, 3% and 3% of subjects in the peginterferon alfa + ribavirin 24 weeks, sofosbuvir + ribavirin 12 weeks and sofosbuvir + ribavirin 24 weeks groups, respectively. Bilirubin levels peaked during the first 1 to 2 weeks of treatment and subsequently decreased and returned to baseline levels by post-treatment week 4. These bilirubin elevations were not associated with transaminase elevations

Creatine Kinase Elevations
Creatine kinase was assessed in the FISSION and NEUTRINO trials. Isolated, asymptomatic creatine kinase elevation of greater than or equal to 10xULN was observed in less than 1%, 1% and 2% of subjects in the peginterferon alfa + ribavirin 24 weeks, sofosbuvir + peginterferon alfa + ribavirin 12 weeks and sofosbuvir + ribavirin 12 weeks groups, respectively

Lipase Elevations
Isolated, asymptomatic lipase elevation of greater than 3xULN was observed in less than 1%, 2%, 2%, and 2% of subjects in the sofosbuvir + peginterferon alfa + ribavirin 12 weeks, sofosbuvir + ribavirin 12 weeks, sofosbuvir + ribavirin 24 weeks and peginterferon alfa + ribavirin 24 weeks groups, respectively

DRUG INTERACTIONS:
Potentially Significant Drug Interactions
Sofosbuvir is a substrate of drug transporter P-gp and breast cancer resistance protein (BCRP) while the predominant circulating metabolite GS-331007 is not. Drugs that are 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 concomitant use with sofosbuvir is not recommended

Information on potential drug interactions with sofosbuvir is summarized in table below:

Potentially Significant Drug Interactions: Alteration in Dosage or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction[a]

Concomitant Drug Class: Drug Name	Effect on Concentration[b]	Clinical Comment
Antiarrhythmics: amiodarone	Effect on amiodarone and sofosbuvir concentrations unknown	Coadministration of amiodarone with sofosbuvir in combination with another DAA may result in serious symptomatic bradycardia. The mechanism of this effect is unknown. Coadministration of amiodarone with sofosbuvir in combination with another DAA is not recommended; if coadministration is required, cardiac monitoring is recommended
Anticonvulsants: carbamazepine phenytoin phenobarbital oxcarbazepine	• sofosbuvir • GS-331007	Coadministration of sofosbuvir with carbamazepine, phenytoin, phenobarbital or oxcarbazepine is expected to decrease the concentration of sofosbuvir, leading to reduced therapeutic effect of sofosbuvir Coadministration is not recommended
Antimycobacterials: rifabutin rifampin rifapentine	• sofosbuvir • GS-331007	Coadministration of sofosbuvir with rifabutin or rifapentine is expected to decrease the concentration of sofosbuvir, leading to reduced therapeutic effect of sofosbuvir. Coadministration is not recommended Coadministration of sofosbuvir with rifampin, an intestinal P-gp inducer, is not recommended
Herbal Supplements: St. John's wort (Hypericum perforatum)	• sofosbuvir • GS-331007	Coadministration of sofosbuvir with St. John's wort, an intestinal P-gp inducer, is not recommended
HIV Protease Inhibitors: tipranavir / ritonavir	• sofosbuvir • GS-331007	Coadministration of sofosbuvir with tipranavir / ritonavir is expected to decrease the concentration of sofosbuvir, leading to reduced therapeutic effect of sofosbuvir. Coadministration is not recommended

a) This table is not all inclusive
b) • = decrease

Drugs without Clinically Significant Interactions with sofosbuvir
In addition to the drugs included in table listed above, the interaction between sofosbuvir and the following drugs was evaluated in clinical trials and no dose adjustment is needed for either drug cyclosporine, darunavir/ritonavir, efavirenz, emtricitabine, methadone, oral contraceptives, raltegravir, rilpivirine, tacrolimus, or tenofovir disoproxil fumarate

USE IN SPECIFIC POPULATIONS:
Pregnancy Category B: There are no adequate and well-controlled studies with sofosbuvir in pregnant women. Because animal reproduction studies are not always predictive of human response, sofosbuvir should be used during pregnancy only if the potential for benefit justifies the potential risk to the fetus

If sofosbuvir is administered with ribavirin or peginterferon and ribavirin, the combination regimen is contraindicated in pregnant women and in men whose female partners are pregnant. Refer to the ribavirin and/or peginterferon prescribing information for more information on use in males and females of child-bearing potential

Animal Data
No effects on fetal development have been observed in rats and rabbits at the highest doses tested. In the rat and rabbit, AUC exposure to the predominant circulating metabolite GS-331007 increased over the course of gestation from approximately 5- to 10-fold and 12- to 28-fold the exposure in humans at the recommended clinical dose, respectively

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. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for sofosbuvir and any potential adverse effects on the breastfed child from the drug or from the underlying maternal condition

If sofosbuvir is administered in a regimen containing ribavirin, the information for ribavirin with regard to nursing mothers also applies to this combination regimen. Refer to the ribavirin prescribing information for more information on use in nursing mothers

Paediatric Use
Safety and effectiveness of sofosbuvir 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 dosage adjustment of sofosbuvir is warranted in geriatric patients

Renal Impairment
No dosage 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 less than 30mL/min/1.73m^2) or ESRD requiring hemodialysis. No dosage recommendation can be given for patients with severe renal impairment or ESRD

Hepatic Impairment
No dosage 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. See peginterferon alfa prescribing information for contraindication in hepatic decompensation

Patients with Hepatocellular Carcinoma Awaiting Liver Transplantation

Post-Liver Transplant Patients: The safety and efficacy of sofosbuvir have not been established in post-liver transplant patients

Patients with Genotype 5 or 6 HCV Infection: Available data on subjects with genotype 5 or 6 HCV infection are insufficient for dosing recommendations

OVERDOSAGE:
The highest documented dosage of sofosbuvir was a single dose of sofosbuvir 1200mg (three times the recommended dosage) administered to 59 healthy subjects. In that trial, there were no untoward effects observed at this dosage level, and adverse events were similar in frequency and severity to those reported in the placebo and sofosbuvir 400mg treatment groups. The effects of higher dosages 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

STABILITY:
See expiry on the pack

PRESENTATION:
OCVIR™ 400mg tablets in a pack of 28's

INSTRUCTIONS:
Keep out of reach of children
Avoid exposure to heat, light and humidity
Store between 15 to 30°C
Improper storage may deteriorate the medicine

اوکور™ ۴۰۰ ملی گرام
(سوفوسبیور) ٹیبلٹ

خوراک: ڈاکٹر کی ہدایت کے مطابق استعمال کریں

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دوا کو دھوپ، گرمی اور نمی سے محفوظ ۱۵ سے ۳۰ ڈگری سینٹی گریڈ

کے درمیان میں رکھیں ورنہ دوا خراب ہو جائیگی

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210 mm

150 mm