ינואר 2020

הודעה על עדכון עלונים:

Harvoni film coated tablets

(sofosbuvir / ledipasvir)

רופאים ורוקחים נכבדים,

חברת גיליאד סיאנסז ישראל בע"מ מבקשת להודיעכם כי חל עדכון בעלון לרופא ובעלון לצרכן של התכשיר בנדון בנובמבר 2019 המובא לידיעתכם.

ההתוויה הרשומה לתכשיר בישראל:

Harvoni is indicated for the treatment of chronic hepatitis C (CHC) in adults.

השינויים מסומנים בעלון המצורף כאשר הטקסט המודגש באדום הוסף לעלון ואילו הטקסט המחוק ~~בקו חוצה~~ נגרע ממנו. הסימונים בצהוב הינם החמרות במידע הבטיחותי.

העדכונים המשמעותיים ביותר מופיעים במכתב זה, קיימים עדכונים מינוריים נוספים.

העלונים לרופא ולצרכן נשלחו לפרסום במאגר התרופות שבאתר משרד הבריאות:

https://data.health.gov.il/drugs/index.html#/byDrug

כמו כן ,ניתן לקבלם מודפסים על ידי פנייה לבעל הרישום:

גיליאד סיאנסז ישראל בע"מ, רחוב החרש 4 ,ת.ד. 6090, פארק העסקים הוד השרון 4524075, ישראל.

התכשיר משווק ע"י חברת סל"א.

בברכה,

מריה חורגין

רוקחת ממונה

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העדכונים המהותיים בעלון לרופא:

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.
Co-administration with rosuvastatin (see section 4.5).

Use with ~~potent~~ strong P-gp inducers

Medicinal products that are ~~potent~~ strong P glycoprotein (P-gp) inducers in the intestine (carbamazepine, phenobarbital, phenytoin, rifampicin, rifabutin~~,~~ and St. John's wort ~~[Hypericum perforatum], carbamazepine, phenobarbital and phenytoin~~). Co-~~-~~administration will significantly decrease ledipasvir and sofosbuvir plasma concentrations and could result in loss of efficacy of Harvoni (see section 4.5).

4.5 Interaction with other medicinal products and other forms of interaction

As Harvoni contains ledipasvir and sofosbuvir, any interactions that have been identified with these active substances individually may occur with Harvoni.
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Potential for other medicinal products to affect Harvoni

Ledipasvir and sofosbuvir are substrates of drug transporter P-gp and BCRP while GS-331007 is not.

Medicinal products that are ~~potent~~ strong P-gp inducers (carbamazepine, phenobarbital, phenytoin, rifampicin, rifabutin~~,~~ and St. John's wort~~, carbamazepine, phenobarbital and phenytoin~~) may significantly decrease ledipasvir and sofosbuvir plasma concentrations leading to reduced therapeutic effect of ledipasvir/sofosbuvir and thus are contraindicated with Harvoni (see section 4.3). Medicinal products that are moderate P-gp inducers in the intestine (e.g. oxcarbazepine) may decrease ledipasvir and sofosbuvir plasma concentrations leading to reduced therapeutic effect of Harvoni. Co-administration with such medicinal products is not recommended with Harvoni (see section 4.4). Co-administration with medicinal products that inhibit P-gp and/or BCRP may increase ledipasvir and sofosbuvir plasma concentrations without increasing GS 331007 plasma concentration; Harvoni may be co administered with P-gp and/or BCRP inhibitors. Clinically significant medicinal product interactions with ledipasvir/sofosbuvir mediated by CYP450s or UGT1A1 enzymes are not expected.

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Table 3: Interactions between Harvoni and other medicinal products

Medicinal product by therapeutic areas	**Effects on medicinal product levels. Mean ratio (90% confidence interval) for AUC, C_{max}, C_{min}[a, b]**	**Recommendation concerning co-administration with Harvoni**
ANTICONVULSANTS		
~~Carbamazepine~~ Phenobarbital Phenytoin	Interaction not studied. *Expected:* ↓ Ledipasvir ↓ Sofosbuvir ↔GS-331007 (Induction of P-gp)	Harvoni is contraindicated with ~~carbamazepine,~~ phenobarbital and phenytoin~~, potent intestinal P-gp inducers~~ (see section 4.3).
Carbamazepine	Interaction not studied *Expected:* ↓ Ledipasvir *Observed:* Sofosbuvir ↓ C_{max} 0.52 (0.43, 0.62) ↓ AUC 0.52 (0.46, 0.59) C_{min} (NA)	Harvoni is contraindicated with carbamazepine (see section 4.3).

	GS 331007 ↔ C_{max} 1.04 (0.97, 1.11) ↔ AUC 0.99 (0.94, 1.04) C_{min} (NA) (Induction of P-gp)	
ANTIMYCOBACTERIALS		
Rifampicin (600 mg once daily)/ ledipasvir (90 mg single dose)[d]	Interaction not studied. *Expected:* Rifampicin ↔ C_{max} ↔ AUC ↔ C_{min} *Observed:* Ledipasvir ↓ C_{max} 0.65 (0.56, 0.76) ↓ AUC 0.41 (0.36, 0.48) (Induction of P-gp)	Harvoni is contraindicated ~~-~~with rifampicin~~, a potent intestinal P-gp inducer~~ (see section 4.3).
Rifampicin (600 mg once daily)/ sofosbuvir (400 mg single dose)[d]	Interaction not studied. *Expected:* Rifampicin ↔ C_{max} ↔ AUC ↔ C_{min} *Observed:* Sofosbuvir ↓ C_{max} 0.23 (0.19, 0.29) ↓ AUC 0.28 (0.24, 0.32) GS-331007 ↔ C_{max} 1.23 (1.14, 1.34) ↔ AUC 0.95 (0.88, 1.03) (Induction of P-gp)	
Rifabutin	Interaction not studied. *Expected:* ↓ Ledipasvir *Observed:* Sofosbuvir ↓ C_{max} 0.64 (0.53, 0.77) ↓ AUC 0.76 (0.63, 0.91) C_{min} (NA) GS 331007 ↔ C_{max} 1.15 (1.03, 1.27) ↔ AUC 1.03 (0.95, 1.12) C_{min} (NA) (Induction of P-gp)	Harvoni is contraindicated with rifabutin (see section 4.3).
~~Rifabutin~~ Rifapentine	Interaction not studied. *Expected:* ↓ Ledipasvir ↓ Sofosbuvir ↔ GS-331007 (Induction of P-gp)	~~Harvoni is contraindicated with rifabutin, a potent intestinal P-gp inducer (see section 4.3).~~ Co-administration of Harvoni with rifapentine is expected to decrease the concentration of ledipasvir and sofosbuvir, leading to reduced therapeutic effect of Harvoni. Such co-administration is not recommended.