רופא/ה נכבד/ה,

רוקח/ת נכבד/ה,

Maviret

מבירט

Film coated tablets

Glecaprevir 100 mg / pibrentasvir 40 mg

חברת AbbVie Biopharmaceuticals Ltd. מבקשת להודיע כי העלונים לרופא ולצרכן של התכשיר עודכנו. בהודעה זו מצוינים סעיפים בהם נעשה שינוי מהותי או שינוי המהווה החמרה (שינוי שהינו הוספה מסומן בקו תחתון, מחיקה מסומנת בקו אמצעי). עדכונים נוספים אשר אינם מהווים החמרה או שאינם מהותיים, אינם נכללים בהודעה זו.

ההתוויה המאושרת לתכשיר:

Maviret is indicated for the treatment of chronic hepatitis C virus (HCV) infection in adults

<u>העלון לצרכן עודכן בסעיף הבא:</u>

4. <u>תופעות לוואי</u>

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<u>תופעות לוואי ששכיחותן אינה ידועה (תופעות ששכיחותן טרם נקבעה)</u>

- <u>גרד</u>

<u>העלון לרופא עודכן בסעיף הבא:</u>

4.8. Undesirable effects

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Tabulated summary of adverse reactions

The following adverse reactions were identified in patients treated with Maviret. The adverse reactions are listed below by body system organ class and frequency. Frequencies are defined as follows: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000) ~~or~~, very rare (< 1/10,000) <u>or not known (cannot be estimated from the available data).</u>

Table 4: Adverse reactions identified with Maviret

Frequency	**Adverse reactions**
Nervous system disorders	
Very common	headache
Gastrointestinal disorders	
Common	diarrhoea, nausea
<u>Skin and subcutaneous tissue disorders</u>	
<u>Not known</u>	<u>pruritus</u>
General disorders and administration site conditions	
Very common	fatigue
Common	asthenia

<u>Description of selected adverse reactions</u>

Adverse reactions in subjects with severe renal impairment including subjects on dialysis

The safety of Maviret in subjects with chronic kidney disease (~~Stage 4 or Stage 5~~ including subjects on dialysis) and genotypes 1, 2, 3, 4, 5 or 6 chronic HCV infection with compensated liver disease (with or without cirrhosis) was assessed in EXPEDITION-4 (n=104) ~~subjects (EXPEDITION-4)~~ and EXPEDITION-5 (n=101). The most common adverse reactions in subjects with severe renal impairment were pruritus (17%) and fatigue (12%) in EXPEDITION-4 and pruritus (14.9%) in EXPEDITION-5.

5.1. Pharmacodynamic properties

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Table 7: Clinical studies conducted with Maviret in subjects with HCV genotype 1, 2, 3, 4, 5 or 6 Infection

Genotype (GT)	Clinical study	Summary of study design
TN and TE subjects without cirrhosis		
GT1	ENDURANCE-1[a]	Maviret for 8 weeks (n=351) or 12 weeks (n=352)
	SURVEYOR-1	Maviret for 8 weeks (n=34)
GT2	ENDURANCE-2	Maviret (n=202) or Placebo (n=100) for 12 weeks
	SURVEYOR-2[b]	Maviret for 8 weeks (n=199) or 12 weeks (n=25)
GT3	ENDURANCE-3	Maviret for 8 weeks (n=157) or 12 weeks (n=233) Sofosbuvir + daclatasvir for 12 weeks (n=115)
	SURVEYOR-2	Maviret for 8 weeks (TN only, n=29) or 12 weeks (n=76) or 16 weeks (TE only, n=22)
GT4, 5, 6	ENDURANCE-4	Maviret for 12 weeks (n=121)
	SURVEYOR-1	Maviret for 12 weeks (n=32)
	SURVEYOR-2[c]	Maviret for 8 weeks (n=58)
TN and TE subjects with cirrhosis		
GT1, 2, 4, 5, 6	EXPEDITION-1	Maviret for 12 weeks (n=146)
GT3	SURVEYOR-2[d]	Maviret for 12 weeks (TN only, n=64) or 16 weeks (TE only, n=51)
Subjects with CKD stage 3b, 4 and 5 with or without cirrhosis		
GT1-6	EXPEDITION-4	Maviret for 12 weeks (n=104)
GT1-6	EXPEDITION-5	Maviret for 8 weeks (n=84) or 12 weeks (n=13) or 16 weeks (n=4)
NS5A inhibitor and/or PI-experienced subjects with or without cirrhosis		
GT1, 4	MAGELLAN-1[e]	Maviret for 12 weeks (n=66) or 16 weeks (n=47)
HCV/HIV-1 Co-Infected Subjects with or without Cirrhosis		
GT1-6	EXPEDITION-2	Maviret for 8 weeks (n=137) or 12 weeks (n=16)

TN=treatment naïve, TE=treatment experienced (includes previous treatment that included pegIFN (or IFN), and/or RBV and/or sofosbuvir), PI=Protease Inhibitor, CKD=chronic kidney disease

a. Included 33 subjects co-infected with HIV-1.

b. GT2 from SURVEYOR-2 Parts 1 and 2 - Maviret for 8 weeks (n=54) or 12 weeks (n=25); GT2 from SURVEYOR-2 Part 4 - Maviret for 8 weeks (n=145).

c. GT3 without cirrhosis from SURVEYOR-2 Parts 1 and 2 - Maviret for 8 weeks (n=29) or 12 weeks (n=54); GT3 without cirrhosis from SURVEYOR-2 Part 3 - Maviret for 12 weeks (n=22) or 16 weeks (n=22).

d. GT3 with cirrhosis from SURVEYOR-2 Part 2 - Maviret for 12 weeks (n=24) or 16 weeks (n=4); GT3 with cirrhosis from SURVEYOR-2 Part 3 - Maviret for 12 weeks (n=40) or 16 weeks (n=47).

e. GT1, 4 from MAGELLAN-1 Part 1 - Maviret for 12 weeks (n=22); GT1, 4 from MAGELLAN-1 Part 2 - Maviret for 12 weeks (n=44) or 16 weeks (n=47).

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Clinical Study in Renally Impaired Subjects

EXPEDITION-5 was an open-label study in 101 HCV GT1-6 infected subjects without cirrhosis or with compensated cirrhosis and chronic kidney disease (CKD) stage 3b, 4, or 5. Subjects were either treatment-naïve or treatment-experienced to combinations of (peg) interferon, ribavirin, and/or sofosbuvir and received Maviret for 8, 12, or 16 weeks per approved treatment durations.

Of the 101 subjects treated, the median age was 58 years (range 32-87); 53% had HCV genotype 1; 27% had HCV genotype 2; 15% had HCV genotype 3; 4% had HCV genotype 4; 59% were male; 73% were White; 80% were HCV treatment-naïve; 13% had cirrhosis and 65% had a baseline fibrosis state of F0 or F1; 7% were CKD stage 3b; 17% were CKD Stage 4, and 76% were CKD Stage 5 (all receiving dialysis); 84 subjects received 8 weeks of treatment, 13 subjects received 12 weeks of treatment, and 4 subjects received 16 weeks of treatment.

The overall SVR12 rate was 97% (98/101). There were no virologic failures.

5.3. Preclinical safety data

Glecaprevir and pibrentasvir were not genotoxic in a battery of *in vitro* or *in vivo* assays, including bacterial mutagenicity, chromosome aberration using human peripheral blood lymphocytes and *in vivo* rodent micronucleus assays. Carcinogenicity studies with glecaprevir and pibrentasvir have not been conducted.

No effects on mating, female or male fertility, or early embryonic development were observed in rodents at up to the highest dose tested. Systemic exposures (AUC) to glecaprevir and pibrentasvir were approximately 63 and 102 times higher, respectively, than the exposure in humans at the recommended dose.

In animal reproduction studies, no adverse developmental effects were observed when the components of Maviret were administered separately during organogenesis at exposures up to 53 times (rats; glecaprevir) or 51 and 1.5 times (mice and rabbits, respectively; pibrentasvir) ~~higher than~~ the human exposures at the recommended dose of Maviret. Maternal toxicity (anorexia, lower body weight, and lower body weight gain) with some embryofoetal toxicity (increase in post-implantation loss and number of resorptions and a decrease in mean foetal body weight), precluded the ability to evaluate glecaprevir in the rabbit at clinical exposures. There were no developmental effects with either compound in rodent peri/postnatal developmental studies in which maternal systemic exposures (AUC) to glecaprevir and pibrentasvir were approximately 47 and 74 times ~~higher~~, respectively, ~~than~~ the exposure in humans at the recommended dose. Unchanged glecaprevir was the main component observed in the milk of lactating rats without effect on nursing pups. Pibrentasvir was the only component observed in the milk of lactating rats without effect on nursing pups.

העלונים המעודכנים לרופא ולצרכן נשלחו למאגר התרופות שבאתר משרד הבריאות, וניתן לקבלם מודפסים על ידי פניה לבעל הרישום, AbbVie Biopharmaceuticals Ltd, רחוב החרש 4, הוד השרון או בטלפון 7909600 – 09.

בברכה,
אינה רגצקי - רוקחת ממונה