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 העלון לרופא של התכשיר שבנדון עודכן.

בהודעה זו מצוינים סעיפים בהם נעשה שינוי מהותי או שינוי המהווה החמרה. מידע שהתווסף מסומן באדום ומידע שהוסר מסומן ~~בכחול~~. 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 and in adolescents aged 12 to <18 years.

העלון לרופא עודכן בסעיף הבא:

4.4 Special warnings and precautions for use

Patients who failed a prior regimen containing an NS5A- and/or an NS3/4A-inhibitor

Genotype 1-infected (and a very limited number of genotype 4-infected) patients with prior failure on regimens that may confer resistance to glecaprevir/pibrentasvir were studied in ~~the~~ studies MAGELLAN-1 ~~study~~ and B16-439 (section 5.1). The risk of failure was, as expected, highest for those exposed to both classes. A resistance algorithm predictive of the risk for failure by baseline resistance has not been established. Accumulating double class resistance was a general finding for patients who failed re-treatment with glecaprevir/pibrentasvir in MAGELLAN-1. No re-treatment data is available for patients infected with genotypes 2, 3, 5 or 6. Maviret is not recommended for the re-treatment of patients with prior exposure to NS3/4A- and/or NS5A-inhibitors.
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5.1 Pharmacodynamic properties

Studies in subjects with or without compensated cirrhosis who were treatment-experienced to NS3/4A protease and/or NS5A inhibitors

Ten of 113 subjects treated with Maviret in the MAGELLAN-1 study for 12 or 16 weeks experienced virologic failure.

Among the 10 genotype 1-infected subjects with virologic failure, treatment-emergent NS3 substitutions V36A/M, R155K/T, A156G/T/V, or D168A/T were observed in 7 subjects. Five of the 10 had combinations of V36M, Y56H, R155K/T, or D168A/E in NS3 at baseline and post-treatment. All of the genotype 1-infected virologic failure subjects had one or more NS5A substitutions L/M28M/T/V, Q30E/G/H/K/L/R, L31M, P32 deletion, H58C/D, or Y93H at baseline, with additional treatment-emergent NS5A substitutions M28A/G, P29Q/R, Q30K, H58D, or Y93H observed in 7 of the subjects at the time of failure.

Thirteen of the 177 subjects with chronic HCV GT1 infection (all virologic failures had GT1a infection) who were treatment experienced with NS5A inhibitor + SOF treated with Maviret in study B16-439 for 12 weeks (9 out of 13) or 16 weeks (4 out of 13) experienced virologic failure. Among the 13 virologic failures, treatment-emergent NS3 substitutions were observed in 4 subjects at the time of failure: A156V (n = 2) or R155W + A156G (n = 2); 3 of these 4 subjects also had Q80K at baseline and at the time of failure. Twelve of 13 virologic failures had one or more NS5A polymorphisms detected at signature amino acid positions (M28V/T, Q30E/H/N/R, L31M/V, H58D, E62D/Q, or Y93H/N) at baseline, and 10 of 13 developed additional NS5A substitutions (M28A/S/T (n = 3), Q30N (n = 1), L31M/V (n = 2), P32del (n = 1), H58D (n = 4), E62D (n = 1)) at time of treatment failure.
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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 PRS-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)
	ENDURANCE-5,6	Maviret for 8 weeks (n=75)
	SURVEYOR-1	Maviret for 12 weeks (n=32)
	SURVEYOR-2[c]	Maviret for 8 weeks (n=58)
GT1-6	VOYAGE-1[f]	Maviret for 8 weeks (GT1, 2, 4, 5, and 6 and GT3 TN) (n=356) or 16 weeks (GT3 TE only) (n=6)
TN and PRS-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)
GT5, 6	ENDURANCE-5,6	Maviret for 12 weeks (n=9)
GT1-6	VOYAGE-2[f]	Maviret for 12 weeks (GT1, 2, 4, 5, and 6 and GT3 TN) (n=157) or 16 weeks (GT3 TE only) (n=3)
GT1-6	EXPEDITION-8	Maviret for 8 weeks (n=343) (TN only)
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)
GT1	B16-439	Maviret for 12 weeks (n=78) or 16 weeks (n=78) or Maviret + RBV for 12 weeks (n=21)[g]
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)
Liver or Kidney Transplant Recipients		
GT1-6	MAGELLAN-2	Maviret for 12 weeks (n=100)
Adolescent subjects (12 to <18 years)		
GT1-6	DORA (Part 1)	Maviret for 8 weeks (n=44) or 16 weeks (n=3)

TN=treatment naïve, PRS 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).
f. VOYAGE-1 and VOYAGE-2 were Asian regional studies.
g. Maviret is not recommended for the re-treatment of patients with prior exposure to NS3/4A- and/or NS5A-inhibitors (see section 4.4).

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Durability of Sustained Virologic Response
In a long-term follow-up study (M13-576), 99.5% (374/376) of adult subjects who had achieved SVR12 in prior clinical studies of Maviret maintained SVR up to their last follow-up visit (median duration of follow-up: 35.5 months): 100%, 99.6%, and 95.8% of subjects who had received 8, 12, and 16 weeks of Maviret therapy, respectively. Among the 2 subjects who did not maintain SVR, 1 experienced a late relapse 390 days after Maviret therapy, and the other subject experienced re-infection with a different HCV genotype.

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העלון המעודכן לרופא נשלח לפרסום במאגר התרופות שבאתר משרד הבריאות, וניתן לקבלו מודפס על ידי פניה לבעל הרישום, AbbVie Biopharmaceuticals Ltd., רחוב החרש 4, הוד השרון או בטלפון 09 – 7909600.

בברכה,
אינה רגצקי - רוקחת ממונה