

## Peginterferon/Ribavirin-Experienced, Genotype 4 Patients Without Cirrhosis

Recommended and alternative regimens listed by evidence level and alphabetically for:

### Peginterferon/Ribavirin-Experienced, Genotype 4 Patients Without Cirrhosis

RECOMMENDED	DURATION	RATING 
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, A
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) <sup>a</sup>	8 weeks	I, B
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) for patients who experienced virologic relapse after prior peginterferon/ribavirin therapy	12 weeks	Ila, B
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)	12 weeks	Ila, B
ALTERNATIVE	DURATION	RATING 
Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus weight-based ribavirin	12 weeks	I, A
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) plus weight-based ribavirin for patients with prior on-treatment virologic failure (failure to suppress or breakthrough) while on peginterferon/ribavirin	16 weeks	Ila, B

<sup>a</sup> This is a 3-tablet coformulation. Please refer to the prescribing information.

## Recommended Regimens

### Sofosbuvir/Velpatasvir

The double-blind, placebo-controlled ASTRAL-1 trial evaluated treatment-naive or -experienced patients with genotype 1, 2, 4, 5, or 6 infection treated with a daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks ([Feld, 2015](#)). The study included 116 patients with genotype 4 infection. One hundred percent SVR12 was achieved, including 52 treatment-experienced patients ([Feld, 2015](#)).

### Glecaprevir/Pibrentasvir

The phase 2, open-label, single arm SURVEYOR-II, part 4 study investigated the efficacy of 8 weeks of the daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) administered as three 100 mg/40 mg fixed-dose

combination pills in patients with genotype 2, 4, 5, or 6 infection without cirrhosis. Patients were treatment naive or experienced (interferon or peginterferon  $\pm$  ribavirin, or sofosbuvir plus ribavirin  $\pm$  peginterferon). Forty-six genotype 4-infected patients accounted for 23% of the study population; only 27 of these patients (13% of the study population) were treatment experienced. The SVR12 was 93%; 3 patients had nonvirologic outcomes, including missed follow-up and study discontinuation. There were no virologic failures but the number of treatment-experienced patients is small ([Asselah, 2018b](#)).

## Elbasvir/Grazoprevir $\pm$ Ribavirin

A 2015 integrated analysis of all phase 2 and phase 3 elbasvir (50 mg)/grazoprevir (100 mg) studies to date demonstrated efficacy of this regimen for both treatment-naive (n=66) and -experienced (n=37) patients with genotype 4 infection ([Asselah, 2018c](#)). The overall SVR12 rate among treatment-experienced, genotype 4-infected patients was 87% (32/37) with numerical response differences based on prior interferon treatment response (relapse vs on-treatment viral failure); elbasvir/grazoprevir duration (12 weeks vs 16 weeks); and/or ribavirin usage (inclusion or exclusion of ribavirin in the regimen). Numbers within any specific subgroup are too small to make definitive recommendations. However, trends emerged that were used to guide the current recommendations pending additional data. No treatment failures were seen in patients who relapsed after prior peginterferon/ribavirin therapy, regardless of elbasvir/grazoprevir treatment duration or ribavirin usage. In contrast, response rates were numerically lower in patients with prior on-treatment virologic failure in the non-ribavirin-containing arms (12 weeks, 78%; 16 weeks, 60%) compared to ribavirin-containing treatment (12 weeks with ribavirin, 91%; 16 weeks with ribavirin, 100%).

Given the lack of sufficient numbers to differentiate response between 12 weeks with ribavirin and 16 weeks with ribavirin, the use of 16 weeks of elbasvir/grazoprevir plus ribavirin in genotype 4-infected patients with prior on-treatment virologic failure represents the most conservative approach.

## Ledipasvir/Sofosbuvir

In the open-label cohort, phase 2a SYNERGY trial, 21 patients with genotype 4 infection were treated with a 12-week course of the daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg). Forty percent of participants were treatment experienced and 40% had advanced fibrosis. Twenty patients completed the 12-week therapy and all achieved SVR12; 1 patient withdrew from the study ([Kohli, 2015](#)). A pooled analysis of the 12-week ledipasvir/sofosbuvir regimen (including the SYNERGY trial) reported an SVR12 rate of 94% (32/34) in treatment-experienced patients with genotype 4 infection ([Asselah, 2018b](#)).

## Alternative Regimen

### Paritaprevir/Ritonavir/Ombitasvir + Ribavirin

PEARL-I was an open-label, phase 2b study that included a cohort of 49 noncirrhotic, treatment-experienced patients (peginterferon/ribavirin) with genotype 4 infection who received 12 weeks of the daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus weight-based ribavirin. Based on intention-to-treat analysis, SVR12 was achieved in 100% of these patients. The regimen was well tolerated with no serious adverse events reported ([Hézode, 2015](#)).

The phase 3, open-label, partly randomized AGATE-II trial enrolled genotype 4-infected, treatment-naive or -experienced (interferon-based therapy) patients, without cirrhosis or with compensated cirrhosis. The 100 noncirrhotic participants were treated with 12 weeks of paritaprevir/ritonavir/ombitasvir plus weight-based ribavirin. The SVR12 in this group of patients was 94% (94/100) ([Esmat, 2015a](#)).

These data support the use of paritaprevir/ritonavir/ombitasvir plus ribavirin for 12 weeks in treatment-experienced, genotype 4-infected patients. Due to the need for ribavirin resulting in a greater pill burden and adverse events profile, this regimen is an alternative recommendation.

**Last update:** September 21, 2017

## Related References

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Esmat GE, Doss WH, Qaqish RB, et al. [Efficacy and Safety of Co-Formulated Ombitasvir/Paritaprevir/Ritonavir with Ribavirin in Adults with Chronic HCV Genotype 4 Infection in Egypt \(AGATE-II\) \[Abstract 708\]](#). In: *66th Annual Meeting of the American Association for the Study of Liver Diseases (AASLD), November 13-17, 2015*. 66th Annual Meeting of the American Association for the Study of Liver Diseases (AASLD), November 13-17, 2015. San Francisco, CA; 2015.

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Kohli A, Kapoor R, Sims Z, et al. [Ledipasvir and sofosbuvir for hepatitis C genotype 4: a proof-of-concept, single-centre, open-label phase 2a cohort study](#). *The Lancet. Infectious Diseases*. 2015;15(9):1049 - 1054.