


## PEG-IFN/Ribavirin Experienced, Genotype 4 Patients Without Cirrhosis

| Recommended Regimens by evidence level and alphabetically for:   |          |  |
|--|----------|--|
| Genotype 4, PEG-IFN/Ribavirin Treatment-experienced Patients, Without Cirrhosis  |          |  |
| RECOMMENDED  | DURATION | RATING  |
| Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) and weight-based ribavirin   | 12 weeks | I, A   |
| Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)   | 12 weeks | I, A   |
| Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg); for patients who experienced virologic relapse after prior PEG-IFN/ribavirin therapy  | 12 weeks | IIa, B   |
| <hr/>  |          |  |
| Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) and weight-based ribavirin; for genotype 4 patients with prior on-treatment virologic failure (failure to suppress or breakthrough) while on PEG-IFN/ribavirin | 16 weeks | IIa, B   |
| Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)   | 12 weeks | IIa, B   |

### Paritaprevir/ritonavir/ombitasvir

PEARL-I was an open-label phase IIb study that included a cohort of 49 treatment-experienced patients with HCV genotype 4 infection without cirrhosis who received 12 weeks of paritaprevir, ritonavir, and ombitasvir (PrO) with or without weight-based ribavirin. In intention-to-treat analysis, SVR12 was achieved in 41 of 41 (100%) patients. This regimen was well tolerated with no serious adverse events reported ([Hézode, 2015](#)). The AGATE-II trial offered 100 treatment-naïve and -experienced noncirrhotic patients with genotype 4 PrO plus weight-based ribavirin for 12 weeks. The SVR12 was 94%. These data continue to support the use of PrO plus ribavirin for 12 weeks in treatment-experienced genotype 4 patients ([Esmat, 2015a](#)).

### Ledipasvir/sofosbuvir

In the SYNERGY trial, 20 patients with HCV genotype 4 infection were treated with ledipasvir/sofosbuvir for 12 weeks. Of these patients, 40% were treatment-experienced and 40% had advanced fibrosis. Preliminary data demonstrate efficacy, with 95% achieving SVR12 based on an intention-to-treat analysis ([Kohli, 2015](#)).

### Sofosbuvir/velpatasvir

Velpatasvir is also active in vitro against genotype 4 and the combination of sofosbuvir/velpatasvir for 12 weeks was

evaluated in 116 genotype 4-infected patients included in the ASTRAL-1 study ([Feld, 2015](#)). 100% SVR12 was achieved, including 52 treatment-experienced patients.

## Elbasvir/grazoprevir

An integrated analysis of all phase 2/3 elbasvir/grazoprevir studies demonstrated efficacy of this regimen for both treatment-naive (n=66) and -experienced (n=37) patients with genotype 4 HCV infection ([Asselah, 2015](#)). 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) and elbasvir/grazoprevir duration (12 vs 16 weeks) and/or ribavirin usage (no ribavirin vs ribavirin). Numbers within any specific subgroup are too small to make definitive recommendation; 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 PEG-IFN/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 + ribavirin: 91%, 16 weeks + 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 plus ribavirin in genotype 4-infected patients with prior on-treatment virologic failure represents the most conservative approach.

## Mixed genotypes

Rarely, genotyping assays may indicate the presence of a mixed infection (eg, genotypes 1a and 2). Treatment data for mixed genotypes with direct-acting antivirals are sparse but utilization of a pangenotypic regimen should be considered. When the correct combination or duration is unclear, expert consultation should be sought.

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