# LMMG New Medicine Recommendation

## Eltrombopag (Revolade ®)

### For treatment of thrombocytopenia in adults with hepatitis C

**LMMG Recommendation:**
Eltrombopag is recommended as an option for the treatment of thrombocytopenia **only** in adults with non-genotype 1 HCV infection who have MELD scores < 10 and baseline albumin >35g/L.

The efficacy and safety of eltrombopag have not been established in combination with direct acting antiviral agents used as standard care in patients infected with genotype 1 HCV. Efficacy in clinical trial participants with MELD scores ≥10 and baseline albumin ≤35g/L was more modest, and these patients were at two- to three fold greater risk for thromboembolic events and hepatic decompensation than in the wider trial population.

**Summary of supporting evidence:**

- Large phase 3 trials have demonstrated the ability of eltrombopag to elevate platelet counts in thrombocytopenic HCV patients to defined levels where they can initiate and maintain peginterferon antiviral therapy. Statistically significantly more patients maintained on eltrombopag achieved sustained virological response (SVR) 24 weeks after completing antiviral therapy compared with patients maintained on placebo (NNT of 13 across all patients in key trials); however absolute rates achieving SVR were low (19-23%).
- It is unclear that the trials reflect the likely use of eltrombopag in clinical practice. Although the platelet count thresholds required for peginterferon initiation (90,000 or 100,000/micrL) and dose reduction / discontinuation were aligned with their SPCs, experienced clinicians may use lower thresholds.[9,13,15] This would bias the trials in favour of eltrombopag, as patients randomised to placebo would stop or reduce antiviral dose sooner than may happen in practice. In addition, as all patients had received eltrombopag and achieved platelet counts of 90,000 or 100,000/micrL before entering the comparative maintenance phase, the placebo arm would not reflect standard care in practice. The net impact of these considerations is unclear.
- Dual antiviral therapy was used for all patients in the trials as this was the standard of care at the time the trials commenced. However, recent guidelines now recommend the use of triple antiviral therapy (i.e. addition of a direct acting antiviral agent to PEG 2a or 2b plus ribavirin) in patients infected with genotype 1 HCV, as this leads to higher SVR in this patient group .[6,16,17] As over 60% of patients in the trials were infected with genotype 1 HCV, the majority of trial participants were not treated with the current standard of care. The SPC notes that the safety and efficacy of eltrombopag have not been established in combination with direct acting antiviral agents approved for treatment of chronic hepatitis C infection.[1]
- The benefits of eltrombopag over placebo were modest in patients with advanced chronic liver disease defined by low albumin levels ≤ 35g/L or MELD score ≥ 10, especially for those with baseline albumin ≤35g/L (NNT approx. 33).
- Rates of hepatic decompensation and thromboembolic events were increased in patients

maintained on eltrombopag. Most patients in the trials had cirrhosis and may be at risk of hepatic decompensation when receiving alfa interferon therapy. Therefore, it is suggested that higher rates of hepatic decompensation observed with eltrombopag could be due to it enabling greater exposure to PEG 2a or 2b.[1,9] Elevated risks of thromboembolic events, particularly portal vein thrombosis, have been documented in other trials.[1] Risks of adverse events were particularly elevated in those with advanced chronic liver disease defined by low albumin levels ≤ 35g/L or MELD score ≥ 10, especially for those with baseline albumin ≤35g/L.

- SMC concluded that eltrombopag was a cost effective treatment when eltrombopag was supplied at a discount price. It is not clear that the SMC analyses would reflect the cost effectiveness of eltrombopag in practice in England.
- Eltrombopag is the only available treatment for thrombocytopenia that is preventing optimal antiviral therapy in patients with chronic HCV. It has the potential to permit achievement of a SVR, which in some patients would be considered to be a cure.
- Eligible patients numbers across Lancashire are anticipated to be low, but eltrombopag is a high cost drug.

## Details of Review

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| **Name of medicine** (generic & brand name):<br><br>Eltrombopag (Revolade®) |
| **Strength(s) and Form(s):**<br><br>25 mg and 50 mg film-coated tablets |
| **Licensed indication(s):**<br><br>Eltrombopag is indicated in adult patients with chronic hepatitis C virus (HCV) infection for the treatment of thrombocytopenia, where the degree of thrombocytopenia is the main factor preventing the initiation or limiting the ability to maintain optimal interferon-based therapy.[1] |
| **Reason for Review:**<br><br>Horizon scanning |
| **Proposed use** (if different from or in addition to licensed indication above):<br><br>n/a |

## Background and context

Hepatitis C virus (HCV) is acquired primarily through percutaneous exposure to contaminated blood. People infected with HCV are often asymptomatic, but in approximately 80% of people who are infected, the virus is not cleared and they go on to develop chronic hepatitis C and liver damage. Progression from mild to severe disease is slow but variable, taking about 20 to 50 years from the time of infection. About 30% of infected people develop cirrhosis within 20 to 30 years, and some of these develop hepatocellular carcinoma (HCC). Some people with end-stage liver disease or hepatocellular carcinoma may require liver transplantation.[3]

Antiviral treatment aims to clear the virus from the blood. Successful treatment is usually indicated by a sustained virological response (SVR), which is defined as undetectable serum HCV RNA six months after the end of treatment. A SVR is considered to indicate permanent resolution of infection, although relapse may occur in approximately 5% of people after 5 years.[3] In addition, in patients with cirrhosis, eradication of HCV reduces the rate of decompensation and HCC, but does not eliminate the risk.[6]

Peginterferon alfa-2a (PEG 2a) or peginterferon alfa-2b (PEG 2b) are antivirals recommended by NICE for treating chronic hepatitis C, alone or in combination with ribavirin, depending on clinical circumstances. [3-5] Triple therapy, involving the addition of direct acting antivirals boceprevir or telaprevir is recommended in patients with HCV genotype 1.[6,16,17] The recommended duration of treatment is 24 or 48 weeks depending on the HCV genotype, viral load at the start of treatment and whether a person has a rapid virological response to treatment.[3,6]

Thrombocytopenia (low platelet count) is a common complication of chronic HCV infection[10] and a haematological side effect of PEG and ribavirin antiviral therapy.[6,7,8] A minimum platelet count is recommended for the initiation and maintenance of anti-viral therapy.[7,8] Therefore, when

thrombocytopenia occurs, it may prevent optimal antiviral therapy and lower the chances of achieving a SVR.

Eltrombopag is an oral, non-peptide, thrombopoietin receptor agonist that activates proliferation and differentiation of bone marrow progenitor cells resulting in increased platelet counts. It has recently been licensed for use in adult patients with chronic HCV infection for the treatment of thrombocytopenia, where this is the main factor preventing initiation or maintenance of optimal interferon-based therapy.[1] Eltrombopag is a high cost drug and was identified for LMMG review via horizon scanning.

## Evidence in Proposed Use

### Summary of Efficacy Data in Proposed Use:

This evidence review is based on two similar phase 3, randomised, placebo-controlled trials of eltrombopag (ENABLE 1 and 2)[9] (Table 1). These enrolled adults with chronic HCV infection and compensated liver disease, who had baseline platelet counts <75,000/microL. The majority were cirrhotic and had genotype 1 HCV. Around a third of patients had previously received antiviral treatment.

The trials consisted of 2 parts. In part 1, all enrolled patients initiated open-label eltrombopag at escalating doses for 2 to 9 weeks to achieve platelet counts of 90,000/microL (ENABLE 1, n=716) or 100,000/microL (ENABLE 2, n=805) as recommended for initiation peginterferon-2a (PEG 2a) or -2b (PEG 2b) treatment, respectively. Around 95% of patients achieved these thresholds and entered the double-blind, part 2 maintenance phase of the trial. In part 2, patients in the ENABLE 1 trial were randomised (2:1) to either continue eltrombopag or receive placebo, both alongside antiviral therapy with PEG-2a plus ribavirin at the recommended licensed doses. Patients in the ENABLE 2 trial were randomised (2:1) to either continue eltrombopag or receive placebo, both alongside antiviral therapy with PEG-2b plus ribavirin. Treatment duration was 24 weeks (for HCV genotype 2/3) or 48 weeks (all other genotypes). If platelet counts declined to <50,000/microL, the dose of PEG 2a or 2b had to be reduced, and if platelet counts declined to <25,000/microL , PEG 2a or 2b had to be discontinued.

Statistically significantly more patients maintained on eltrombopag achieved the primary endpoint of SVR at 24 weeks after completing antiviral treatment compared with placebo in both ENABLE 1 (23% vs. 14%; p=0.0064; NNT 11) and ENABLE 2 (19% vs. 13%; p=0.02; NNT 17). Eltrombopag maintained platelet counts above 50,000/microL for more patients than placebo, and across both trials statistically significantly fewer patients discontinued antiviral therapy while taking eltrombopag (45% vs. 60%; p<0.0001).[1,9]

Benefits in SVR were observed across pre-specified subgroups based on baseline platelet counts (<50,000 or ≥50,000/microL), baseline viral load (<800,000 or ≥800,00IU/mL) and HCV genotype (2/3 or non-2/3); however, the benefit of eltrombopag over placebo was numerically lower in patients with non-2/3 HCV genotypes (SVR 15% vs. 8%; difference 7%) than in those with HCV genotypes 2/3 (35% vs. 25%; difference 10%).[1] Post hoc analyses indicated that, compared with the group overall, the benefits of eltrombopag over placebo were modest in patients with advanced chronic liver disease defined by low albumin levels ≤ 35 g/L or MELD score ≥ 10, especially for those with baseline albumin ≤35g/L (SVR 11% vs. 8%; difference 3%).[1]

### Other Efficacy data:

Other efficacy data are limited to a small, double-blind, 12-week, phase 2, dose finding-study that randomised 74 patients with baseline platelet counts of 20,000 to 70,000/microL to receive eltrombopag at doses of 30mg, 50mg or 75mg daily, or placebo.[11] This study demonstrates the efficacy of eltrombopag in raising platelet counts to at least 100,000/microL by 4 weeks but adds little over the data above.

**Summary of Safety Data:**

In the initiation phase of the ENABLE trials, 1% of patients in both the eltombopag and placebo arms experienced a severe adverse event. This increased to 20% and 15%, respectively in the maintenance phase.[9]

The SPC notes the most important serious adverse reactions identified with eltrombopag were hepatotoxicity and thrombotic/thromboembolic events (TEE).[1] Hepatic decompensation (ascites, hepatic encephalopathy, variceal haemorrhage, spontaneous bacterial peritonitis) was reported more frequently with eltrombopag treatment than with placebo (11% vs. 6%, respectively), as were TEEs (4% vs. 1%). Portal vein thrombosis was the most common TEE in both treatment groups (2% in patients treated with eltrombopag vs. <1 % for placebo). Patients with low albumin levels (≤35 g/L) or Model for End-Stage Liver Disease (MELD) score ≥ 10 at baseline were at three-fold greater risk of hepatic decompensation and two-fold greater risk of TEEs. TEEs were two-fold greater in patients aged 60 years or over compared with younger patients.[1]

A greater proportion of placebo treated patients discontinued investigational product due to an adverse event compared with eltrombopag treated patients (29% vs. 22%). The difference was mainly attributed to thrombocytopenia. Hematological toxicities were the most common reasons for discontinuation in both treatment groups.[10]

Eltrombopag treatment increases treatment duration and exposure to PEG 2a or 2b antiviral therapy, which may contribute to observed increased risks of adverse events.[9]

**Summary of Evidence on Cost Effectiveness and Patient Outcomes:**

The Scottish Medicines Consortium (SMC) accepted eltrombopag for the treatment of patients with thromobocytopenia and chronic HCV as a cost effective use of NHS resources in Scotland based on a cost-utility analysis incorporating a confidential discount on its list price. The analysis compared eltrombopag plus antiviral therapy (consisting of peginterferon in combination with ribavirin) against standard of care (suboptimal or no antiviral therapy). The economic model involved a short-term, antiviral therapy phase, and a longer term phase including the consequences of chronic HCV over a lifetime horizon (for example, stages of fibrosis moving towards decompensated cirrhosis, ascites, liver cancer, liver transplantation, and death). Pooled data from the ENABLE studies was used to model eltrombopag treatment. As placebo recipients in the trials also received eltrombopag prior to antiviral therapy, these data were adjusted with data from the literature to try to reflect more accurately the SoC outcomes in current clinical practice. Quality of life data collected in the ENABLE studies and derived from the literature were used to estimate quality-adjusted life years (QALYs).

The result of the base case analysis, incorporating the discounted price of eltrombopag, was a cost per QALY gained of £22,760, based on an added lifetime cost of £11,320 and a QALY gain of 0.50. A more conservative sensitivity analysis, using alternative adjustments to the ENABLE trial data for placebo-treated patients, resulted in a cost per QALY gained of £29,945 with the discounted price of eltrombopag. It was noted that the ENABLE trials may not accurately reflect current treatment in practice due to the platelet count thresholds employed for initiation of antiviral therapy. Despite these issues, the economic case was considered to have been demonstrated.[13]

Eltrombopag was recommended by NICE TA293 for the treatment of chronic immune (idiopathic) thrombocytopenic purpura on the basis of a patient access scheme that provided a confidential discount on its list price.[14] It is unclear if this discounted price will be applied to eltrombopag for the treatment of thrombocytopenia in HCV, or if the level of discount is the same as that agreed for Scotland in the SMC cost utility analyses.

**Key Points to Note from the Available Evidence:**

- Large phase 3 trials have demonstrated the ability of eltrombopag to elevate platelet counts in thrombocytopenic HCV patients to defined levels where they can initiate and maintain peginterferon antiviral therapy. Statistically significantly more patients maintained on eltrombopag achieved SVR 24 weeks after completing antiviral therapy compared with patients maintained on placebo (NNT of 13 across all patients in key trials); however absolute rates achieving SVR were low (19-23%).
- It is unclear that the trials reflect the likely use of eltrombopag in clinical practice. Although the platelet count thresholds required for peginterferon initiation (90,000 or 100,000/micrL) and dose reduction / discontinuation were aligned with their SPCs, experienced clinicians may use lower thresholds.[9,13,15] This would bias the trials in favour of eltrombopag, as patients randomised to placebo would stop or reduce antiviral dose sooner than may happen in practice. In addition, as all patients had received eltrombopag and achieved platelet counts of 90,000 or 100,000/micrL before entering the comparative maintenance phase, the placebo arm would not reflect standard care in practice. The net impact of these considerations is unclear.
- Dual antiviral therapy was used for all patients in the trials as this was the standard of care at the time the trials commenced. However, recent guidelines now recommend the use of triple antiviral therapy (i.e. addition of a direct acting antiviral agent to PEG 2a or 2b plus ribavirin) in patients infected with genotype 1 HCV, as this leads to higher SVR in this patient group .[6,16,17] As over 60% of patients in the trials were infected with genotype 1 HCV, the majority of trial participants were not treated with the current standard of care. The SPC notes that the safety and efficacy of eltrombopag have not been established in combination with direct acting antiviral agents approved for treatment of chronic hepatitis C infection.[1]
- The benefits of eltrombopag over placebo were modest in patients with advanced chronic liver disease defined by low albumin levels ≤ 35g/L or MELD score ≥ 10, especially for those with baseline albumin ≤35g/L (NNT approx. 33).
- Rates of hepatic decompensation and thromboembolic events were increased in patients maintained on eltrombopag. Most patients in the trials had cirrhosis and may be at risk of hepatic decompensation when receiving alfa interferon therapy. Therefore, it is suggested that higher rates of hepatic decompensation observed with eltrombopag could be due to it enabling greater exposure to PEG 2a or 2b.[1,9] Elevated risks of thromboembolic events, particularly portal vein thrombosis, have been documented in other trials.[1] Risks of adverse events were particularly elevated in those with advanced chronic liver disease defined by low albumin levels ≤ 35g/L or MELD score ≥ 10, especially for those with baseline albumin ≤35g/L.
- SMC concluded that eltrombopag was was cost effective treatment when eltrombopag was supplied at a discount price. It is not clear that the SMC analyses would reflect the cost effectiveness of eltrombopag in practice in England.

**Productivity, Service Delivery and Implementation Considerations:**

Eltrombopag treatment may enable peginterferon antiviral therapy to be used in more patients and for longer periods than would otherwise be possible. This would increase use of antivirals and associated monitoring in eligible patients, although the number of such patients is likely to be small.

**Innovation, Need and Equity Considerations:**

Patients with HCV and thrombocytopenia that precludes optimal antiviral therapy have significant unmet needs. Eltrombopag is the only available treatment to address thrombocytopenia in these patients. It has the potential to permit achievement of a SVR, which in some patients would be

considered to be a cure. Public Health England notes that, beyond the benefits to individual patients, successful treatment may also help to reduce transmission of the virus within the population.[12]

Hepatitis C predominantly affects marginalised groups of society, including people who inject drugs and minority ethnic populations.[12]

## Recommended Place in Therapy

Eltrombopag is recommended as an option for the treatment of thrombocytopenia **only** in adults with non-genotype 1 HCV infection who have MELD scores < 10 and baseline albumin >35g/L.

The efficacy and safety of eltrombopag have not been established in combination with direct acting antiviral agents used as standard care in patients infected with genotype 1 HCV. Efficacy in clinical trial participants with MELD scores $\geq$10 and baseline albumin $\leq$35g/L was more modest, and these patients were at two- to three fold greater risk for thromboembolic events and hepatic decompensation than in the wider trial population.

## Financial and Service Implications

**Comparative unit costs:**

As eltrombopag is the only treatment currently available for thrombocytopenia in HCV infected adults there are no relevant comparators.

The required dose and duration of treatment depend on individual platelet count response and the infecting HCV genotype.[1] The licensed dose range is 25-100mg daily, although 86% of patients in the ENABLE trials required 25-50mg daily and the majority achieved target platelet counts within 4 weeks.[9] Assuming these trial observed doses and initiation phases, the cost of eltrombopag could range from £5,390 for patients requiring 25mg daily for 24 weeks of antiviral therapy, to £19,635 for patients requiring 50mg for 48 weeks. In the few patients requiring maximum dose of 100mg daily, the cost of a course of treatment, assuming dose escalation over 8 weeks followed by 48 weeks maintenance, would theoretically increase to £40,810.

**Anticipated patient numbers and net budget impact:**

The NICE costing template for the technology appraisals of Boceprevir and Telaprevir estimates that 0.5% of adults are infected with HCV, of which 50% are diagnosed. Of these, 82.5% are estimated to develop chronic HCV infection,[18] which would be equivalent to 2,435 cases in Lancashire. Of these, two thirds (1,624) are assumed to be offered treatment.

Estimates of the proportion of patients with chronic HCV infection that develop thrombocytopenia vary widely from 15-70% depending in the definition adopted.[19] The SMC advice on eltromopag reported around 138 cases in Scotland eligible for treatment with eltrombopag each year based on a threshold platelet count of 75,000/microL, and 74 patients per year based on a threshold platelet count of 50,000/microL. Uptake estimated by the company is 70%[13] Crudely applying these figures from the population of Scotland (5.3million) to the population of Lancashire (1.5million) would equate to 27 patients receiving eltrombopag in Lancashire using a threshold platelet count of 75,000/microL, or 15 patients using a threshold platelet count of 50,000/microL.

The budget impact for treating 27 patients per year across Lancashire would range from £145,530 per year at a dose of 25mg for 24 weeks maintenance treatment to £530,145 per year at dose of 50mg for 48 weeks of maintenance treatment.

The budget impact for treating 15 patients per year across Lancashire would range from £80,850 per year at a dose of 25mg for 24 weeks maintenance treatment to £294,525 per year at dose of 50mg for 48 weeks of maintenance treatment.

As the efficacy and safety of eltrombopag has not been demonstrated in combination with direct acting antiviral agents that are recommended as a component of triple therapy for genotype 1 HCV, restricting the use to patients without genotype 1 HCV could be an option. The NICE costing template for the technology appraisals of Boceprevir and Telaprevir estimates that 45% of HCV infections in the UK are of genotype 1. Assuming the same risks of thrombocytopenia across genotypes, restricting eltrombopag use to non-genotype 1 HCV infected patients would decrease the above crude cost estimates by 45%.

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**Table 1. Summary of ENABLE 1 & 2 phase 3 studies of eltrombopag for treating thrombocytopenia in patients with HCV**

| Ref | Trial design | Patients / Trial subjects | Trial intervention and comparison | Outcomes: Primary endpoint (ITT) | Outcomes: Key secondary / exploratory endpoints | Grading of evidence / risk of bias |
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| 1, 2 | Both trials same 2-part design, apart from type of peginterferon and platelet count thresholds for initiation.<br><br>Part 1: Open-label dose escalation phase for 2-9 weeks to achieve platelet thresholds<br><br>Part 2: Double-blind RCT for duration of antiviral therapy (24 to 48 weeks depending on HCV genotype) | Adults<br>Confirmed HCV infection<br>Baseline platelets <75,000/microL.<br>Adequate hepatic, renal and haematological function.<br>Previous therapy permitted if reason for stopping was thrombocytopenia.<br><br>Median age: 52yrs<br>Male: 62-63%<br>White / Asian: 72-75% / 23-24%<br>HCV genotype 1: 62-65%<br>HCV genotype 2/3: 31-33%<br>Child-Pugh score A (5-6): 94-96%<br>Fibrosis/cirrhosis: 78-91%<br>Baseline Platelet count >50,000/microL: 70-73% (median 59,000/microL)<br>HCV titre >800,000IU/mL: 47-51%<br>Prior treatment: ~33%<br><br>Excluded:<br>Previous non- | Part 1:<br>Open-label eltrombopag dose escalation (25mg, 50mg, 75mg, 100mg once daily) to achieve platelet counts ≥90,000/microL (ENABLE 1, n=716) or >100,000/microL (ENABLE 2, n=805)<br><br>Part 2:<br>Eltrombopag at same dose from initiation phase (ENABLE 1 n=450; 396 completed;<br>ENABLE 2 n=506; 404 completed)<br>; or<br>Placebo<br>(ENABLE 1 n=232; 197 completed;<br>ENABLE 2 n=253; 205 completed)<br><br>Both arms in addition to antiviral treatment with PEG 2a 180mcg/week (ENABLE 1) or PEG 2b 1.5mcg/kg/week (ENABLE 2), both plus RBV dosed according to HCV genotype and body weight. Antiviral treatment was for 24 weeks for HCV genotype 2/3 or 48 weeks for other genotypes. | SVR 24 weeks after completing antiviral therapy:<br><br>ENABLE 1:<br>Eltrombopag 23% vs. Placebo 14%; p=0.0064; NNT=11<br><br>ENABLE 2:<br>Eltrombopag 19% vs. Placebo 13%; p=0.0202; NNT=17<br><br>Pooled data:<br>Eltrombopag 21% vs. Placebo 13%; p=0.0202; NNT=13 | 95% patients achieved target platelet thresholds in Part 1. Median time to achieve target 2 weeks.<br><br>Platelet counts above 50,000/microL:<br>ENABLE 1:<br>Eltrombopag 69% vs. Placebo 15%<br><br>ENABLE 2:<br>Eltrombopag 81% vs. Placebo 23%<br><br>Antiviral discontinuations (Pooled data):<br>(Eltrombopag 45 % vs. Placebo 60 %, p = <0.0001).<br><br>Antiviral dose reduction (Pooled data):<br>Eltrombopag 54 % vs. Placebo 73 %; p-value not reported | Allocation concealment?: Yes for Part 2, Part 1 was non-randomised, open-label<br><br>Blinded if possible?: Yes, double-blind phase in Part 2. Open-label in Part 1<br><br>Intention to treat analysis?: Yes<br><br>Adequate power/size?: Yes, power calculations presented<br><br>Adequate follow-up (>80%)?: Yes<br><br>Other forms of bias: Yes. Bias in trial design in favour of eltrombopag: Dose reduction / discontinuation of antivirals based on higher platelet thresholds than likely used in practice has potential to artificially elevate response with eltrombopag over placebo to greater degree than could be seen in practice. Bias in trial design in favour of placebo: All patients randomised to |

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| | | responders to PEG +RBV if not related to thrombocytopenia<br>Decompensated liver disease<br>Serious CVD or pulmonary disease<br>History of thromboembolic events<br>Hepatitis B or HIV infection<br>Bleeding conditions or need for anticoagulation. | | | | placebo had received eltrombopag to achieve platelet counts >90,000/microL and were treated with antivirals, so not reflective of patients on standard of care in practice.<br><br>Level 3 evidence based on lack of patient-orientated outcomes. |
| CVD=Cardiovascular disease; HCV=hepatitis C virus; ITT=Intension to treat; PEG=Peginterferon alfa; RBV=Ribavirin; SVR=Sustained virologicalresponse (defined as undetectable HCV-RNA)<br>Grading of evidence / risk of bias based generally on SORT definitions of high quality randomised controlled trials. | | | | | | |



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