Protease inhibitors (Boceprevir and telaprevir) in the treatment of chronic HCV infection: relative efficacy, safety and efficiency (Executive summary)

Drug assessment report

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Executive summary

Title
Protease inhibitors (Boceprevir and telaprevir) in the treatment of chronic HCV infection: relative efficacy, safety and efficiency.

Objectives
1. To evaluate the efficacy of each protease inhibitor (PI) with standard bitherapy versus standard bitherapy and to evaluate the relative efficacy of boceprevir vs. telaprevir in adult patients with untreated chronic hepatitis C virus (HCV) genotype 1 infection.
2. To evaluate the efficacy of each PI with standard bitherapy versus standard bitherapy and to evaluate the relative efficacy of boceprevir vs. telaprevir in adult patients with previously treated chronic HCV genotype 1 infection.
3. To evaluate the safety of each PI with standard bitherapy versus standard bitherapy and to evaluate the relative safety of boceprevir vs. telaprevir in untreated and previously treated adult patients with chronic HCV genotype 1 infection.
4. To evaluate the efficiency of each PI in untreated and previously treated adult patients with chronic HCV genotype 1 infection.
5. To estimate the budgetary impact of adding boceprevir or telaprevir to the standard treatment on the Andalusian Public Health System.

Methodology
To accomplish evidence-based response to efficacy and safety objectives, randomized clinical trials (RCT) of each PI were considered. Trials were located through the assessment report from the European Medicines Agency (EMA). A critical evaluation of the studies was performed. Furthermore, to evaluate safety, the data base FEDRA was consulted.

Studies regarding adult patients with chronic HCV genotype 1 infection, either naïve or previously treated were included in the efficacy and safety assessment. Patients received a PI with peginterferon–ribavirin therapy vs. peginterferon–ribavirin therapy. The rate of sustained virologic response (SVR), response at end of therapy, rate of relapse, viral breakthrough, adverse events and withdrawals due to adverse events were evaluated. Included design studies were phase III RCT, and also phase II RCT, only in the safety assessment.

Critical appraisal, data extraction and qualitative synthesis were conducted, independently, by two researchers. Critical appraisal, quality assessment, and potential sources of bias for the individual studies were performed by means of CASPe questionnaires (Critical Appraisal Skills Programme).

To evaluate the relative efficacy and safety, high quality head to head RCT are
needed. In absence of those trials, indirect comparisons analyses were performed. The method of Bucher et al. for adjusted indirect comparisons was used to make the estimations. The SIGN calculator and the software of the Canadian Agency for Drugs and Technologies in Health (CADTH) for adjusted indirect comparisons version 1.0 were used. In the cases where statistically significant differences between each PI and its control group in a particular outcome were observed, adjusted indirect comparisons were conducted. In efficacy outcomes, indirect comparisons were only performed with SVR.

An exhaustive search of the economic published literature in referential data sources and a critical evaluation of the data submitted by the industry were performed. Furthermore, the rates of cost per NNT and of cost per cured patient with each PI were calculated taking into account the results of the efficacy assessment. The Health System perspective was used in the analyses, considering only the direct costs of the drugs. Moreover, the annual budgetary impact on the Andalusian Public Health System was calculated for the incorporation of one PI to the treatment in adult patients with chronic HCV genotype 1 infection.

**Efficacy and safety results**

**Efficacy results**

Three RCT were included in the efficacy assessment of boceprevir, one of them in naïve patients (SPRINT-2) and two in previously treated patients (RESPOND-2 and P05685AM2). Two RCT were included in the efficacy assessment of telaprevir, one of them in naïve patients (ADVANCE) and the other one in previously treated patients (REALIZE). Likewise, the assessment report from the EMA of each PI was considered.

In naïve patients (SPRINT-2 RCT), SVR was significantly higher in each group of triple therapy with boceprevir versus standard treatment [63% group with response-guided therapy (RGT) and 66% BOC44 group vs. 38% control group]. In the subgroup analyses, SVR was significantly higher among patients receiving a boceprevir-containing regimen than among controls for patients with fibrosis F0/F1/F2 (SVR F0/F1/F2: 71% and 67% vs. 40% and SVR F2: 61% and 68% vs. 29% for the RGT, BOC44 and control group, respectively). In regard to the data taking into account the Interleukin-28B polymorphism, there were no significant differences in term of SVR between the groups in patients with CC genotype. However, there were significant differences between groups for the genotypes CT and TT (SVR genotype CT: 65% and 71% vs. 28%, and SVR genotype TT: 55% and 59% vs. 27%, RGT, BOC44 and control groups, respectively). In patients with undetectable viral load in week 4, there were no significant differences between triple therapy with boceprevir and standard treatment (SVR: 89%, 90% and 97% RGT and BOC44 groups versus control group, respectively).

In naïve patients (ADVANCE RCT), efficacy in terms of SVR was significantly higher in each group of triple therapy with boceprevir versus standard treatment [63% group with response-guided therapy (RGT) and 66% BOC44 group vs. 38% control group]. In the subgroup analyses, SVR was significantly higher among patients receiving a boceprevir-containing regimen than in control group for patients with minimal fibrosis, portal fibrosis and bridging fibrosis (SVR minimal fibrosis: 81% vs. 46%, SVR portal fibrosis: 75% vs. 48% and SVR bridging fibrosis: 62% vs. 33%, T12PR group and control group, respectively). There were also significant differences in terms of SVR between each experimental group and the control group in all the analyses performed considering the IL28B polymorphism (SVR genotype CC: 90% vs. 64%, SVR genotype
In patients with undetectable plasmatic viral load in week 4, standard treatment with peginterferon–ribavirin was significantly higher in control group than in telaprevir-containing regimen (SVR: 84% vs. 94% T12PR and control group, respectively).

In patients who do not have a sustained response to therapy with peginterferon–ribavirin (RESPOND-2 RCT), there were significantly higher SVR rates in boceprevir groups than in control group, in patients with prior relapse, and in patients with non-response to previous treatment. In patients with prior relapse, SVR was 59%, 66% vs. 21% and in patients with non-response, SVR was 40%, 52% vs. 7%, for RGT, BOC44, and control groups, respectively. In the analysis performed taking into account the grade of fibrosis, there were significant differences in terms of SVR between BOC44, and control group, for patients with F0/F1, F2 and F3/F4 fibrosis (SVR_{F0/F1}: 70% vs. 25%, SVR_{F2}: 64 vs. 15%, and SVR_{F3/F4}: 68 vs. 13%, for BOC44, and control groups, respectively).

In the analysis of subgroups of response to previous treatment in the RCT REALIZE, SVR was significantly higher in the telaprevir group (T12PR48) than in the control group, in patients with prior relapse (SVR 83% vs. 24%), patients with partial response (SVR 59% vs. 15%) and patients without response to previous therapy (SVR 29% vs. 5%). In the subgroup of patients with previous relapse, there were significant differences in terms of SVR between the experimental groups and control group, independently of genetic polymorphism and of the grade of fibrosis (SVR minimal fibrosis: 85% vs. 35%, SVR portal fibrosis: 81% vs. 28%, and SVR cirrhosis and bridging fibrosis: 84% vs. 13%, T12PR48, and control group, respectively). In the subgroup of patients with prior partial response and prior null response, there were no significant differences in SVR between groups either in genetic polymorphism, or in the grade of fibrosis. The number of patients included in those subgroups was small to allow the detection of differences between them.

**Safety results**

1,548 patients treated with boceprevir and 547 patients treated with standard therapy were analyzed in the safety assessment. Those patients were included in two phase III RCT (SPRINT-2 and RESPOND-2), and one phase II RCT (SPRINT-1). Statistically significant differences were observed between boceprevir and control groups in anaemia (49% vs. 29%), neutropenia (23% vs. 18%), dysgeusia (37% vs. 15%), vomiting (18% vs. 11%), and diarrhoea (23% vs. 18%). Moreover, statistically significant differences were observed between groups in the following adverse effects of grade 4 and higher: anaemia (7% vs. 3%), neutropenia (30% vs. 17%), and thrombocytopenia (3% vs. 1%).

The safety profile of telaprevir was based on aggregated data available from three phase II RCT, and two phase III RCT (ADVANCE y REALIZE). 1,823 patients treated with telaprevir and 764 patients treated with standard therapy were analyzed in the safety assessment. Telaprevir group showed a significantly higher grade of anaemia (36% vs. 18%), and any grade rash (36% vs. 23%). Furthermore, there were significant differences
between groups in the following adverse events (grade 3 or higher): anaemia (5% vs. 1%), thrombocytopenia (1% vs. 0.1%), rash (2% vs. 0.1%), and pruritus (1% vs. 0.1%).

**Relative efficacy of the protease inhibitors**

In the adjusted indirect treatment comparisons analyses, no differences were observed between boceprevir and telaprevir, in relation to SVR, in naïve adult patients (RR: 0.98, 95 CI%: 0.80-1.20). No differences were observed between both PI in the subgroups of patients without fibrosis, neither portal fibrosis with few septa, nor portal fibrosis with septa (RR: 1.07, 95 CI%: 0.86-1.32, boceprevir RGT vs. telaprevir T12PR).

In the adjusted indirect treatment comparisons analyses, no differences were observed between boceprevir (RGT) and telaprevir (T12PR), in terms of SVR, in prior relapse patients (RR: 0.66, 95 CI%: 0.35-1.22), and in prior partial response patients (RR: 1.47, 95 CI%: 0.28-7.72).

In relation to any grade of anaemia and anaemia defined as haemoglobin < 8.5g/dl, no differences were detected between boceprevir (RGT), and telaprevir (T12PR) (RR: 0.86, 95 CI%: 0.68-1.10 y RR: 0.65, 95 CI%: 0.31-1.65, respectively), based on adjusted indirect treatment comparisons analyses.

**Efficiency results**

There is no evidence regarding direct comparison of both PI. The results of the study performed by Lui et al. in terms of cost utility for each PI showed that using the less expensive PI in advanced fibrosis patients, the therapy could be considered cost-effective.

The reports about boceprevir from the Scottish Medicines Consortium showed that boceprevir is a cost-effective drug. The Canadian Drug Expert Committee pointed out that the cost of the treatment with boceprevir could be above $ 100,000 per quality adjusted life year, mainly in patients with mild fibrosis.

Regarding telaprevir, all the publications analysed, except one abstract, showed that telaprevir is a cost-effective drug.

The data provided by the industry only allow to conclude that, in the cases where comparisons have been made, boceprevir had a lower cost than telaprevir.

**Cost per NNT, cost per patient and budgetary impact**

The cost per number needed to treat (NNT) for the addition of telaprevir or boceprevir to the standard treatment in naïve patients was € 100,940, and € 73,052, respectively. In prior relapse patients, it was € 51,200, and € 60,225, and in partial response patients, it was € 5,705 and € 60,225, respectively. Null responder patients were only included in the RCT REALIZE and the cost per NNT for the addition of telaprevir was € 126,176.

The cost per cured patient for the addition of telaprevir or boceprevir to the standard treatment in naïve patients was € 33,647 and € 28,097. In prior relapse patients, it was € 30,843 and € 27,882 and in partial response patients, it was € 42,771 and
€ 43,641, respectively. In null responder patients, the cost per cured patient with telaprevir was € 87,017.

In Andalusia, the incorporation of one PI to the standard treatment would imply an annual increase in the expenses of hospital pharmacy of 6.94%, in the case that all the patients were treated with telaprevir, and 5.43%, in the case of being treated with boceprevir. The incorporation of one PI to the standard treatment of adult patients with chronic HCV genotype 1 infection only in patients with grade of fibrosis F3 and F4 would imply an annual increase in the the expenses of hospital pharmacy of 2.53% with telaprevir, and 1.98% with boceprevir.

**Conclusions**

*Efficacy of the protease inhibitors in adult patients with chronic infection with hepatitis C virus genotype 1*

**Naïve patients**

- Boceprevir with standard treatment increases the efficacy in terms of SVR in naïve patients.
- According to subgroups, boceprevir with standard treatment increases the efficacy in terms of SVR in naïve patients with genetic polymorphism IL28B CT and TT, and in patients without fibrosis, with portal fibrosis without septa and portal fibrosis with few septa.
- Triple therapy with boceprevir is as effective as standard therapy in terms of SVR in naïve patients with undetectable plasmatic viral load in week 4.
- Telaprevir with standard treatment increases the efficacy in terms of SVR in naïve patients.
- According to subgroups, telaprevir with standard treatment increases the efficacy in terms of SVR in naïve patients independently of the genetic polymorphism IL28B, and telaprevir increases the efficacy in patients without fibrosis, minimal fibrosis, bridging fibrosis and advanced fibrosis.
- Standard treatment is more effective than triple therapy with telaprevir in terms of SVR in naïve patients with undetectable plasmatic viral load in week 4.

**Pretreated patients**

- Boceprevir with standard treatment increases the efficacy in terms of SVR in prior relapse patients.
- Boceprevir with standard treatment increases the efficacy in terms of SVR in prior partial response patients.
- Null patients were not included in the RCT RESPOND-2.
- According to subgroups, boceprevir with standard treatment increases the efficacy in terms of SVR, in previously treated patients independently of the grade of fibrosis and in patients with genetic polymorphism IL28B CT.
- Telaprevir with standard treatment increases the efficacy in terms of SVR in prior...
relapse patients.

- According to subgroups, in prior relapse patients, telaprevir with standard treatment increases the efficacy in terms of SVR, independently of the grade of fibrosis and the genetic polymorphism IL28B CT.
- Telaprevir with standard treatment increases the efficacy in terms of SVR, in prior partial response patients.
- Telaprevir with standard treatment increases the efficacy in terms of SVR, in null response patients to previous treatment.

**Safety of the protease inhibitors**

- In naïve patients, as well as in previously treated patients, boceprevir with standard treatment increases the rate of dysgeusia. Moreover, boceprevir increases the rate of anaemia, neutropenia and thrombocytopenia of grade 3 and higher grade.
- In naïve patients, as well as in previously treated patients, telaprevir with standard treatment increases the rate of dysgeusia, thrombocytopenia, rash and pruritus of grade 3 and higher grade.

**Relative efficacy and safety of protease inhibitors**

*Based on adjusted indirect comparisons analyses:*

- There are no differences in terms of SVR between boceprevir and telaprevir in naïve patients. In the subgroup of patients without fibrosis, portal fibrosis with few septa and without septa, there were no differences in terms of SVR between both PI.
- There are no differences in terms of SVR between boceprevir and telaprevir in prior relapse patients.
- There are no differences in terms of SVR between boceprevir and telaprevir in prior partial response patients.
- Regarding to any grade of anaemia and patients with Hb < 8.5g/dl, there are no differences between boceprevir and telaprevir, either in naïve patients or in previously treated patients.

**Efficiency**

- In the economic evaluations analyzed, both PI are considered cost-effective drugs. Incremental cost-effective ratios are more favourable for patients with worse basal status and patients treated with response guided therapy.
- Boceprevir has a cost per NNT more favourable for naïve patients and prior partial response patients, whereas telaprevir has a cost for NNT more favourable for prior relapse patients. Null responder patients are only included in the RCT REALIZE (telaprevir), and not in the RCT RESPOND-2 (boceprevir).
The budgetary impact of adding to the standard treatment a PI in 2012, if only advanced fibrosis and cirrhosis patients are considered for the treatment (F3 and F4), would be approximately €14,460,000 with telaprevir and €11,300,000 with boceprevir. Those data represent an increment of 2.53% and 1.98% of SSPA total pharmacy expenditure, respectively.