

telaprevir, 375mg, film-coated tablets (Incivo®)

SMC No. (742/11)

Janssen

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The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

telaprevir (Incivo®) is accepted for use within NHS Scotland.

Indication under review: In combination with peginterferon alfa and ribavirin, is indicated for the treatment of genotype 1 chronic hepatitis C in adult patients with compensated liver disease (including cirrhosis) who have previously been treated with interferon alfa (pegylated or non-pegylated) alone or in combination with ribavirin, including relapsers, partial responders and null responders.

In the pivotal phase III randomised study, the addition of telaprevir to current standard therapy in patients with genotype 1 chronic hepatitis C virus, who had failed previous therapy, significantly increased the proportion of patients who achieved a sustained virologic response.

Overleaf is the detailed advice on this product.

**Chairman,
Scottish Medicines Consortium**

Indication

In combination with peginterferon alfa and ribavirin, telaprevir is indicated for the treatment of genotype 1 chronic hepatitis C in adult patients with compensated liver disease (including cirrhosis) who are treatment-naïve or who have previously been treated with interferon alfa (pegylated or non-pegylated) alone or in combination with ribavirin, including relapsers, partial responders and null responders.

Dosing Information

750mg (two 375mg tablets) orally every 8 hours with food (total daily dose is 2,250mg (6 tablets)). Taking telaprevir without food or without regard to the dosing interval may result in decreased plasma concentrations of telaprevir which could reduce the therapeutic effect.

Telaprevir should be administered in conjunction with ribavirin and peginterferon alfa-2a or -2b. For specific dosage instructions, the Summary of Product Characteristics (SPC) for these medicinal products should be consulted.

Duration of treatment for prior treatment relapsers

Treatment with telaprevir must be initiated in combination with peginterferon alfa and ribavirin and administered for 12 weeks.

- Patients with undetectable hepatitis C virus ribonucleic acid (HCV RNA) at weeks 4 and 12 receive an additional 12 weeks of peginterferon alfa and ribavirin alone for a total treatment duration of 24 weeks.
- Patients with detectable HCV RNA at either weeks 4 or 12 receive an additional 36 weeks of peginterferon alfa and ribavirin alone for a total treatment duration of 48 weeks.

For all patients with cirrhosis irrespective of undetectable HCV RNA at weeks 4 or 12, an additional 36 weeks of peginterferon alfa and ribavirin alone for a total treatment duration of 48 weeks is recommended.

Duration of treatment for prior partial or null response

Treatment with telaprevir must be initiated in combination with peginterferon alfa and ribavirin and administered for 12 weeks, followed by an additional 36 weeks of peginterferon alfa and ribavirin alone for a total treatment duration of 48 weeks.

Patients with HCV RNA >1,000 IU/mL at week 4 or week 12 are highly unlikely to achieve a sustained virologic response so should discontinue therapy.

Product availability date

26 September 2011

Summary of evidence on comparative efficacy

Telaprevir is a directly-acting antiviral; it inhibits the non-structural 3-4A serine protease which is essential for viral replication. Telaprevir is the second drug in this pharmacological class to be licensed for the treatment of genotype 1 chronic HCV.

This submission considers the use of telaprevir in patients who have failed previous therapy (including relapsers, partial responders and null responders) with interferon alfa (pegylated or non-pegylated) alone or in combination with ribavirin. Separate SMC advice relates to the use of telaprevir in treatment-naive patients.

One pivotal, phase III, randomised, double-blind, placebo-controlled study (REALIZE) assessed the addition of telaprevir to standard therapy in 662 previously treated patients.¹ Patients had previously not responded to, had a partial response or relapsed from a treatment course of peginterferon alfa and ribavirin for genotype 1 HCV. Patients were required to be between 18 and 70 years old, have detectable HCV RNA, a recent liver biopsy and adequate haematopoietic function. Eligible patients were randomised into one of three treatment groups, stratified according to baseline viral load and type of previous response to therapy. The study duration was 72 weeks, including a treatment period of 48 weeks and follow up of 24 weeks.

All patients received peginterferon alfa-2a (180 micrograms per week subcutaneously) and ribavirin (1000 to 1200mg per day orally) for 48 weeks. In addition, patients were randomised to receive either:¹

- T12PR48 (n=266): 12 weeks of telaprevir followed by 4 weeks of placebo (licensed dose);
- Lead-in T12PR48 (n=264): placebo for 4 weeks followed by telaprevir for 12 weeks;
- Control group (n=132): 16 weeks of placebo.

Telaprevir dose was 750mg orally every 8 hours in each active treatment group.

In the active treatment groups, any patient who had HCV RNA levels greater than 100 IU/mL at week 4, 6 or 8 after the start of telaprevir treatment had the telaprevir treatment stopped, and peginterferon alfa and ribavirin continued. All treatment was discontinued in any patient who had a less than a 2 log₁₀ decrease in HCV RNA at week 12 in the T12PR48 and the control groups, or at week 16 in the lead-in T12PR48 group.

The primary outcome was the proportion of patients with either a previous relapse or lack of a previous response (partial response or no response) who achieved a sustained virologic response (SVR) in the intention to treat population. SVR was defined as undetectable HCV RNA 24 weeks after the last planned dose of a study drug. The results for the T12PR48 (licensed telaprevir dose) and control groups are presented below.

In patients who had a previous relapse (n=354), a SVR was achieved by significantly more telaprevir patients: 83% (121/145) and 24% (16/68) in the T12PR48, and control group respectively, p<0.001.¹

In patients who had a prior lack of response (partial or no response, n=308), a SVR was achieved by 41% (50/121) and 9.4% (6/64) respectively, p<0.001. This includes patients who

had a prior partial response (59% [29/49] and 15% [4/27], $p < 0.001$) and those who had no prior response (29% [21/72] and 5.4% [2/37], $p < 0.001$).¹

Overall, a SVR was achieved by 64% (171/266) and 17% (22/132) of patients respectively with a between group difference of 47% (95% confidence interval [CI]: 37 to 57, $p < 0.001$).¹ Higher rates of SVR in the telaprevir groups were maintained in subgroup analyses by stage of liver fibrosis and baseline viral load.¹

In patients who had achieved an undetectable HCV RNA at the end of the assigned treatment, the relapse rates at 72 weeks were 7% (10/135), and 65% (30/46) for the T12PR48 and control groups respectively, in previously relapsed patients. In patients with a prior lack of response the relapse rate was 23% (16/69), and 60% (3/5).¹

Summary of evidence on comparative safety

In the pivotal study (REALIZE), an adverse event was experienced by 98% (260/266) and 95% (126/132) of patients in the T12PR48 and control groups respectively.¹

The most common adverse events experienced by the T12PR48 and control groups were fatigue (55% and 40% respectively), pruritus (52% and 27%), headache (42% and 37%), infections (37% and 36%), rash (37% and 19%), nausea (35% and 23%), influenza-like illness (32% and 25%), anaemia (30% and 15%), insomnia (26% and 26%), diarrhoea (25% and 14%), pyrexia (23% and 27%), cough (23% and 20%) and asthenia (19% and 29%).¹

As the concomitant use of erythropoiesis-stimulating agents was prohibited during the study anaemia was managed by reducing the dose of ribavirin.

Serious adverse events were experienced by 12% (33/266) and 5.3% (7/132) of patients, and treatment was discontinued because of adverse effects by 15% (39/266) and 3.0% (4/132) of patients, in the T12PR48 and control groups respectively.¹

The percentage of patients in the telaprevir group experiencing either a grade 3 skin event, any skin event resulting in permanent discontinuation of any or all study drugs, or any skin event defined as a serious adverse event, was 5% compared with no patients in the control group.¹

Summary of clinical effectiveness issues

The Hepatitis C Action Plan for Scotland estimates that approximately 50,000 people in Scotland are infected with HCV. In the pivotal study, there was an increase in patients achieving a SVR from 17% to 64% when telaprevir was included in the treatment regimen. An increase in patients achieving a SVR should decrease the incidence of onward transmission and risk of developing complications from HCV.

The marketing authorisation for telaprevir includes a response guided therapy, based on the regimen tested in the pivotal phase III study of treatment-naïve patients (ADVANCE).² In the REALIZE study, the subgroup of previously treated HCV patients who had a prior relapse, achieved a SVR of 83%. This high response rate, which was similar to rates achieved in treatment-naïve patients, and low further relapse rate, led to results from treatment-naïve

patients being extrapolated to allow previously relapsed patients to utilise the response guided therapy. Non-cirrhotic relapsed patients treated with telaprevir PR who have undetectable viral load at week 4 and 12 can stop treatment at 24 weeks. This shorter duration of treatment for the patients who have previously relapsed will have benefits for both the patients and the service. However the evidence for stopping early in this group of patients is not as robust as for patients who are treatment-naive.

There was a greater incidence of some adverse events in the telaprevir treatment groups than in the control group. In particular, the increased frequency of skin adverse events will require to be managed appropriately. The SPC provides advice for managing patients with severe rash.

Two telaprevir tablets are required to be taken with food three times a day, in addition to weekly subcutaneous injections of peginterferon alfa and up to seven tablets a day of ribavirin. The high tablet burden may make it difficult for patients to achieve good adherence.

The REALIZE study excluded patients co-infected with hepatitis B and HIV and, while the use of telaprevir is not contra-indicated in these patients, the SPC notes the limitations of the clinical data in these patient groups. However, the exclusion of patients with hepatitis B and HIV is in line with the recommendations from the European Medicines Agency for a step-wise approach to the evaluation of new direct acting antivirals in order to minimize the development of drug-resistance. Patients who had abused alcohol or illicit drugs in the past 2 years were also excluded from the study which may affect the generalisability to the Scottish population.

Boceprevir has also recently been launched for the treatment of chronic hepatitis C infection in combination with peginterferon alfa and ribavirin but there are no comparative efficacy data available.

Summary of comparative health economic evidence

The submitting company presented a cost-utility analysis of 12 weeks of telaprevir in combination with peginterferon alfa and ribavirin (PR) for 48 weeks compared with PR alone for 48 weeks, in patients with HCV genotype 1 infection who have received previous standard therapy. The results were estimated separately according to response to prior PR therapy: prior relapsers, partial responders or null responders. Although peginterferon alfa 2b was not included, the comparator was considered appropriate. A Markov model was used with a lifetime horizon to extrapolate from the relative proportions of patients achieving SVR with telaprevir/PR and PR alone after the first cycle (1 year). Patients started in one of three health states: mild hepatitis C; moderate hepatitis C and compensated cirrhosis; and progressed to more advanced disease states if they had not achieved SVR post-treatment.

The source of the clinical evidence came from the pivotal study in patients who received previous standard therapy. The transition probabilities for the Markov model were taken from various published sources. The utility values used in the model were from a published health technology assessment report where quality of life was measured in patients with HCV using EQ-5D. A utility decrement was included to capture the treatment-related quality of life loss due to adverse events based on EQ-5D data collected in the pivotal telaprevir clinical trial.

Resource use relating to the costs of patient evaluation, initial tests and monitoring associated with treatment were included. In addition, the costs associated with the different health states of

SVR, chronic HCV, compensated cirrhosis, decompensated cirrhosis, hepatocellular carcinoma and liver transplant were included in the model. The resource use estimates included in the submission were taken from published sources used in previous NICE appraisals in HCV.

The submitting company estimated the following results for telaprevir/PR vs PR alone:

Patient group	Incremental cost	Incremental quality adjusted life years (QALYs)	Incremental cost per QALY
All patients	£10,478	1.11	£9,440
Prior relapser patients	£7,555	1.41	£5,363
Prior partial responder patients	£11,085	1.05	£10,558
Null responders	£15,764	0.57	£27,725

The probability of telaprevir being cost-effective at £20k/QALY was estimated to be 91.7%. Cost-effectiveness was greatest in treatment-experienced patients who were prior relapsers, defined as having achieved undetectable HCV RNA at end of previous treatment but which had subsequently become detectable, but was poorest (£27.7K/QALY) in prior null responders to PR treatment. There was only a 27% probability estimated of cost-effectiveness in the null responders at a cost/QALY threshold of £20K, and 54% at a threshold of £30K/QALY. The use of response guided therapy in prior treatment relapsers helped improve estimates of overall cost-effectiveness in this sub-population. The cost-effectiveness of telaprevir/PR also improved according to disease severity at baseline with estimates of £23K/QALY, £9.3K/QALY and £4.8K/QALY for mild, moderate and cirrhosis patient sub-groups respectively.

The results were sensitive to a number of variables. Assuming an upper 95% confidence interval for PR, SVR rate increased the incremental cost-effectiveness ratio (ICER) to £73.6K/QALY for null responders, and to £27K/QALY for prior partial responders. The ICERs were also highly upwardly sensitive to lower SVR for telaprevir/PR, shorter time horizons, and lower utilities for cirrhosis states with SVR. However, a number of variables tested in scenario analysis reduced the ICER to under £20K/QALY for null responders including assuming a lower starting treatment age of 30 years instead of the base case 50 years (£19.6K/QALY), and upper estimates for SVR for telaprevir/PR (£14.6K/QALY).

Despite the relatively high ICER in prior null responders, and sensitivity to some parameters, overall the cost-effectiveness of a standard regimen of telaprevir/PR has been demonstrated in treatment-experienced patients.

Summary of patient and public involvement

Patient Interest Group Submissions were received from:

- Waverly Care
- Hepatitis C Trust

Additional information: guidelines and protocols

Guidelines were published by Scottish Intercollegiate Guidelines Network (SIGN) for the management of hepatitis C in December 2006. The treatment of choice for chronic hepatitis C is 48 weeks of combination treatment with peginterferon alfa and ribavirin. In patients who have not achieved a SVR with non-pegylated interferon with or without ribavirin, retreatment with peginterferon alfa and ribavirin is successful in some patients. The SIGN guidelines predate the availability of telaprevir and other protease inhibitors in hepatitis C treatment.

The European Association for the Study of the Liver (EASL) published "EASL clinical practice guidelines: management of hepatitis C virus infection" in 2011. This recommends the combination of pegylated interferon and ribavirin as the approved standard of care. The duration of treatment can be tailored to the on-treatment virologic response with HCV RNA assessed at baseline, weeks 4 and 12 and also at week 24 in selected patients. The likelihood of SVR is directly proportional to the time of HCV RNA disappearance. The guideline mentions the studies with telaprevir and boceprevir and notes that the guideline will be updated when these combinations are approved.

The Scottish Government has published a Hepatitis C Action Plan for Scotland: Phase I was issued in 2006 and phase II in 2008. There are six strands of work that involve co-ordination of services, prevention, testing, treatment, care and support, education, training and awareness-raising and surveillance and monitoring.

Additional information: comparators

Telaprevir is additional to the current standard treatment of peginterferon alfa and ribavirin. Boceprevir has also recently been launched for add-on therapy to peginterferon alfa and ribavirin.

Cost of relevant comparators

Drug	Dose Regimen	Cost per course (£)
*telaprevir	750mg every 8 hours for 12 weeks	22,398
**boceprevir	800mg three times daily for 32 to 44 weeks	22,400 to 30,800

Doses are for general comparison and do not imply therapeutic equivalence. Both agents are used in combination with peginterferon alfa and ribavirin. The following costs are calculated based on agents and dosing schedules used in the pivotal studies.

*In addition to peginterferon alfa-2a 180 micrograms subcutaneously once weekly and ribavirin 1000mg daily for 24 or 48 weeks according to response guided therapy costing £4,835 or £9,671 respectively. Costs from eVadis on 23 August 2011.

**In addition to pegylated interferon 1.5micrograms per kg subcutaneously weekly plus ribavirin 1000mg daily for 48 weeks costing £9,595. Costs from eVadis on 11 July 2011. Doses based on body weight of 70kg.

Additional information: budget impact

The submitting company estimated the population eligible for treatment to be 2,171 treatment experienced HCV genotype 1 patients in year 1 rising to 3,046 patients in year 5. This represents 13.5% of the estimated number of patients with HCV in Scotland. Based on a forecast uptake of telaprevir/PR of 0.9% in year 1 (18 patients), 5.4% in year 3 (135 patients), decreasing to 0.6% in year 5 (17 patients), the impact on the medicines budget was estimated at £547K in year 1, £4.1 million by year 3, decreasing to £516K in year 5. The net impact after displacement of PR through the use of response guided therapy in prior treatment relapsers was estimated to be £516K in year 1, £3.9 million in year 3, and £488K in year 5. SMC clinical expert responses suggest that uptake rates of the new class of protease inhibitors in hepatitis C infection may be higher than those suggested by the company.

References

The undernoted references were supplied with the submission.

1. Zeuzem S, Andreone P, Pol S et al. Telaprevir for Retreatment of HCV Infection. N Engl J Med 2011;364:2417-28
2. Jacobson IM, McHutchison JG, Dusheiko G et al. Telaprevir for Previously Untreated Chronic Hepatitis C Virus Infection. N Engl J Med 2011; 364:2405-16

This assessment is based on data submitted by the submitting company up to and including 17 October 2011.

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.