

telaprevir 375mg film-coated tablets (Incivo®)

SMC No. (743/11)

Janssen

04 November 2011

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, for the treatment of genotype 1 chronic hepatitis C in adult patients with compensated liver disease (including cirrhosis) who are treatment-naïve.

In the pivotal phase III randomised study, addition of telaprevir to current standard therapy in treatment-naïve patients with genotype 1 chronic hepatitis C virus, significantly increased the proportion of patients who achieved a sustained virologic response, even in patients treated for a shorter overall duration using response-guided therapy.

Overleaf is the detailed advice on this product.

**Chairman,
Scottish Medicines Consortium**

Indication

In combination with peginterferon alfa and ribavirin, 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.

Use of telaprevir in patients who have previously been treated will be considered in a separate submission and separate SMC advice will be issued.

Dosing Information

750mg (two 375mg tablets) should be taken orally every 8 hours with food (the total daily dose is 6 tablets (2,250mg)). 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 of telaprevir.

Telaprevir should be administered in conjunction with ribavirin and either peginterferon alfa-2a or -2b referring to the respective Summary of Product Characteristics (SPC) for dosing recommendations. 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.

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

Treatment with telaprevir should be initiated and monitored by a physician experienced in the management of chronic hepatitis C.

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 treatment-naive patients. Separate SMC advice relates to the use of telaprevir in patients 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.

One phase III, randomised, double-blind, placebo-controlled study (ADVANCE) compared the addition of telaprevir to response guided therapy with peginterferon alfa and ribavirin.¹ Eligible patients were aged between 18 and 70 years, with HCV genotype 1 infection and evidence of chronic hepatitis confirmed by liver biopsy within the previous year, and had received no previous treatment for HCV. Patients with compensated liver cirrhosis were eligible for enrolment. Patients were randomised with stratification by genotype 1 subtype and baseline viral load to receive one of three treatments:¹

- telaprevir for 12 weeks plus peginterferon alfa-2a and ribavirin for 12 weeks. Patients who achieved an extended rapid virologic response (eRVR, undetectable HCV RNA at week 4 and week 12) received a further 12 weeks of peginterferon alfa-2a and ribavirin therapy (total treatment duration of 24 weeks). Patients who did not achieve an eRVR (i.e. had detectable HCV RNA at week 4 or 12) received a further 36 weeks of peginterferon alfa-2a and ribavirin therapy (total treatment duration of 48 weeks) (T12PR).
- telaprevir for 8 weeks plus peginterferon alfa-2a and ribavirin for 12 weeks. Patients who achieved an eRVR received a further 12 weeks of peginterferon alfa-2a and ribavirin therapy (total treatment duration of 24 weeks). Patients who did not achieve an eRVR received a further 36 weeks of peginterferon alfa-2a and ribavirin therapy (total treatment duration of 48 weeks) (T8PR).
- peginterferon alfa-2a and ribavirin for 48 weeks (PR).

Telaprevir was administered at a dose of 750mg orally every 8 hours; peginterferon alfa-2a at a dose of 180micrograms subcutaneously once weekly and ribavirin at a dose of 1,000mg daily in patients <75kg or 1,200mg daily in patients ≥75kg. The study included the following stopping rules:¹

- patients receiving telaprevir who had HCV RNA levels >1,000IU/mL at week 4 stopped telaprevir but continued peginterferon alfa-2a and ribavirin therapy;
- all patients with a reduction of HCV RNA of less than 2 log₁₀ from baseline to week 12 stopped all treatment;
- all patients with detectable HCV RNA between weeks 24 and 40 stopped all treatment.

The primary outcome was the proportion of patients with a sustained virologic response (SVR, defined as undetectable HCV RNA 24 weeks after the last planned dose of a study drug). The results for the T12PR group (licensed dose) and control are presented below. SVR was achieved in significantly more telaprevir treated (T12PR) patients (75% [271/363]) than PR-treated patients (44% [158/361]) with a difference of 31% (95% confidence interval [CI]:24 to 38), p<0.001.¹

The key secondary outcome was the proportion of patients with SVR at 72 weeks (i.e. 24 weeks after the last dose in those treated for 48 weeks and 48 weeks after the last dose in those treated for 24 weeks). This was achieved in significantly more T12PR than PR patients 73% (265/363) versus 44% (158/361) respectively.¹

The duration of treatment was guided by response depending on whether an eRVR had been achieved. An eRVR was achieved in 58% (212/363) T12PR patients, 57% (207/364) T8PR patients and 8% (29/361) PR patients and these patients received only a further 12 weeks of PR therapy to give a total treatment duration of 24 weeks. In these patients an SVR was achieved in 89% (189/212) T12PR group, 83% (171/207) T8PR group and 97% (28/29) PR group.¹

The efficacy of response guided therapy was further evaluated in a randomised, open-label, phase III study (ILLUMINATE).² This tested for non-inferiority in the difference in SVR rates between telaprevir for 12 weeks plus peginterferon alfa-2a and ribavirin for 24 weeks (T12PR24) and telaprevir for 12 weeks plus peginterferon alfa-2a and ribavirin for 48 weeks (T12PR48) in treatment-naïve patients with genotype 1 chronic hepatitis C virus (HCV). Patients who achieved an eRVR at week 20 were randomised to either 24 or 48 weeks of treatment with PR. The primary outcome of SVR was achieved in 92% (149/162) of T12PR24 patients and 88% (140/160) T12PR48 patients corresponding to a difference of 4.5% (95% CI: -2.1% to 11%) which met the pre-specified margins for non-inferiority.²

Summary of evidence on comparative safety

In the ADVANCE study, an adverse event was experienced by 99% (361/363) of patients in the T12PR group and 98% (354/361) of patients in the PR group. Serious adverse events were reported in 9.1% (33/363) and 6.6% (24/361) of patients respectively.¹

The most common adverse events experienced by the patients in the T12PR and PR groups were fatigue (57% and 57%), pruritus (50% and 36%), nausea (43% and 31%), headache (41% and 39%), musculoskeletal disorders in (39% and 50%), rash (37% and 24%), anaemia (37% and 19%), insomnia (32% and 31%) and diarrhoea (28% and 22%).¹

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

Discontinuation of all treatment at some point during the study because of adverse events was reported in 9.9% (36/363) and 7.2% (26/361) of patients respectively. Discontinuation of telaprevir or placebo during the telaprevir/placebo phase because of adverse events was reported in 11% (41/363) and 0.8% (3/361) of patients respectively. These discontinuations were due to rash (6.6% versus 0.6%), anaemia (3.6% versus 0) and pruritus (0.6% versus 0). The difference in mean haemoglobin levels between the two groups reached a maximum of 1.04g/dL at 8 weeks.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 an SVR from 44% to 75% 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 ADVANCE study. Patients who have undetectable viral load at week 4 and 12 stopped treatment at 24 weeks.¹ This shorter duration of treatment for patients will have benefits for both the patients and the service. This was further confirmed in terms of non-inferiority of stopping treatment at 24 weeks or continuing to 48 weeks in the ILLUMINATE study.²

There was a greater incidence of some adverse events in the telaprevir treatment groups in the ADVANCE study.¹ 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 ADVANCE and ILLUMINATE studies excluded patients co-infected with hepatitis B and HIV, and while the use of telaprevir is not contraindicated 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 would appear to be 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 minimise the development of drug-resistance. Patients who had abused alcohol or illicit drugs in the past two years were also excluded from the studies 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 2a and ribavirin (PR) for 48 weeks compared with PR alone for 48 weeks, in patients with HCV genotype 1 infection who were treatment-naïve. 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 a 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 no 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 an incremental cost-effectiveness ratio (ICER) of £14,230 per quality adjusted life year (QALY), consisting of an incremental cost of £11,478 and a 0.81 QALY gain for telaprevir/PR over PR alone. The use of response guided therapy contributed to the overall cost-effectiveness of telaprevir/PR. The cost-effectiveness of telaprevir/PR also improved according to disease severity at baseline, with estimates of £19.3K/QALY, £12.8K/QALY, and £10.6K/QALY for mild, moderate and cirrhosis patient sub-groups respectively.

The ICERs showed some sensitivity to changes in the utility parameters; assuming a 25% lower utility estimate for SVR from a mild hepatitis C starting health state increased the ICER to £33.4K/QALY, whereas using a 25% higher value for the health state reduced it to £9.5K/QALY. A range of £9.4K to £29.1K/QALY was estimated from varying the utility for patients achieving SVR from the moderate hepatitis C health state. The ICER was also reasonably sensitive to telaprevir drug cost with a range of £8K/QALY to £20.4K/QALY when this was varied by $\pm 25\%$.

However, overall the cost-effectiveness of telaprevir/PR in treatment naïve HCV patients has been demonstrated.

Summary of patient and public involvement

Patient Interest Group Submissions were received from:

- Waverly Care
- Hepatitis C Trust

Additional information: guidelines and protocols

The Scottish Intercollegiate Guidelines Network (SIGN) guideline number 92 “Management of hepatitis C: a national clinical guideline” published in December 2006 recommends that a combination of pegylated interferon and ribavirin is the treatment of choice for patients with hepatitis C. SVR should be used as a marker for viral clearance. Patients with HCV genotype 1 should be treated with pegylated interferon and ribavirin for 48 weeks. Patients should be tested for an early virologic response (EVR) at 12 weeks and those who fail to achieve this should be considered for cessation of treatment. Patients who are HCV RNA positive at 24 weeks should be considered for cessation of treatment. 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 orally every 8 hours for 12 weeks	22,398
**boceprevir	800mg three times daily for 24 to 44 weeks	16,800 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 28 weeks costing £5,595. #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 5,756 treatment-naive HCV genotype 1 patients in year 1 rising to 8,077 patients in year 5. This represents 36% of the estimated number of patients with HCV in Scotland. Based on a forecast uptake of telaprevir/PR of 0.04% in year 1 (2 patients), and 5% in year 5 (401 patients), the impact on the medicines budget was estimated at £58K in year 1 and £11.7 million in year 5. The net impact after displacement of PR through the use of response guided therapy was estimated to be £53K in year 1 and £10.6 million 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. The reference shaded grey is additional to those supplied with the submission.

1. 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

2. Sherman KE, Flamm SL, Afdhal NH et al. Response-guided telaprevir combination treatment for hepatitis C virus infection. N Engl J Med 2011;365:1014-24.

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.