Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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daclatasvir 30mg and 60mg film-coated tablets (Daklinza®) SMC No. (1002/14)

Bristol-Myers Squibb

10 October 2014

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

daclatasvir (Daklinza®) is accepted for restricted use within NHS Scotland.

Indication under review: In combination with other medicinal products for the treatment of chronic hepatitis C virus (HCV) infection in adults.

SMC restriction: use is restricted to patients with significant fibrosis (Metavir scores F3-F4) or compensated cirrhosis.

In a phase II study 89% to 99% of patients with genotype 1 and 3 HCV treated with daclatasvir in various peginterferon-free regimens achieved a sustained virological response at 12 weeks (SVR12). In a phase III study of patients with genotype 4 HCV, the superiority of daclatasvir with peginterferon-alfa plus ribavirin (PR) versus placebo + PR was demonstrated for the primary endpoint of SVR12.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Published 10 November 2014

Indication

In combination with other medicinal products for the treatment of chronic hepatitis C virus (HCV) infection in adults.

Dosing Information

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

Daclatasvir 60mg once daily. Daclatasvir must be administered in combination with other medicinal products as follows:

Genotype 1 or 4 without cirrhosis: daclatasvir + sofosbuvir for 12 weeks.

Genotype 1 or 4 with compensated cirrhosis: daclatasvir + sofosbuvir for 24 weeks (consider adding ribavirin for patients with very advanced liver disease or with other negative prognostic factors such as prior treatment experience).

Genotype 3 with compensated cirrhosis and/or treatment experienced: daclatasvir + sofosbuvir + ribavirin for 24 weeks.

Genotype 4: daclatasvir for 24 weeks + peginterferon alfa + ribavirin for 24 to 48 weeks.

Product availability date

29 August 2014

Summary of evidence on comparative efficacy

Daclatasvir is a first-in-class hepatitis C virus nonstructural protein 5A (HCV NS5A) replication complex inhibitor.[1] It was made available by the European Medicines Agency (EMA) for compassionate use in November 2013 and granted marketing authorisation, via an accelerated assessment in September 2014.[2] It is the fifth direct acting antiviral drug marketed in the UK for chronic hepatitis C (CHC); telaprevir and boceprevir are indicated for treatment of genotype 1 HCV, sofosbuvir in genotypes 1 to 6 HCV and simeprevir in genotypes 1 and 4 HCV.[3-6] Daclatasvir, as well as sofosbuvir and simeprevir, may be used as part of peginterferon-free regimens.

An open-label, phase IIa study (AI444-040) was conducted in treatment naive or previously treated patients with CHC and no evidence of cirrhosis.[7-9] Patients who were previously treated had to have failed prior therapy with, or relapsed after, a telaprevir or boceprevir containing regimen. A total of 88 patients who were treatment naive (genotype 1, 2 or 3 HCV) were randomised equally to receive sofosbuvir for one week, then daclatasvir + sofosbuvir for 23 weeks (groups A and B); daclatasvir + sofosbuvir for 24 weeks (groups C and D); or daclatasvir + sofosbuvir + ribavirin for 24 weeks (groups E and F). Following a protocol amendment, an additional 123 patients (genotype 1, treatment naive or failed previous treatment), were randomised equally to receive: daclatasvir + sofosbuvir for 12 weeks (group G); daclatasvir + sofosbuvir + ribavirin for 12 weeks (group H); daclatasvir + sofosbuvir for 24 weeks (group I); or daclatasvir + sofosbuvir + ribavirin for 24 weeks (group J). Daclatasvir was administered orally, 60mg once daily; sofosbuvir was administered orally, 400mg once daily. Ribavirin was administered orally twice daily; in patients with genotype 1 infection, 1,000 to 1,200mg/day,

according to body weight [1,000mg in patients with a body weight of <75kg, and 1,200mg in patients with a body weight ≥75kg]; and in patients infected with genotype 2 or 3, 800mg/day.

The primary outcome was the proportion of patients with SVR12 defined as an HCV RNA level <25 IU/mL at week 12 after the end of treatment. SVR12 was achieved by 98% (124/126) of patients with genotype 1 HCV (treatment naïve), 100% (41/41) with genotype 1 HCV (failed previous treatment), 96% (25/26) with genotype 2 HCV and 89% (16/18) with genotype 3 HCV. Response to treatment was rapid (viral load at week 4 showed that >97% of patients responded to therapy), and was not influenced by HCV subtype (1a/1b), interleukin 28B (IL28B) genotype, or use of ribavirin. Treatment-naïve patients with HCV genotype 1 who received 12 weeks of treatment had a similar response to those treated for 24 weeks. In patients with ≥F3 fibrosis, SVR12 was achieved in 100% (61/61) of patients with genotype 1 HCV, 100% (8/8) of patients with genotype 2 HCV and 100% (5/5) of patients with genotype 3 HCV.

A randomised, double-blind, phase III study (AI444-042) was conducted in treatment-naive patients with CHC (genotype 4 HCV) and an HCV RNA viral load of ≥10,000IU/mL.[8-10] Patients were randomised in a 2:1 ratio to daclatasvir 60mg orally once daily (24 weeks) + PR (peginterferon alfa-2a 180 micrograms subcutaneously once weekly + ribavirin 1,000mg [<75kg] or 1,200mg [≥75kg]) for 24 to 48 weeks) or placebo + PR (doses as before, for 48 weeks). In the daclatasvir group, the length of treatment with PR depended on response; patients who did not have HCV RNA undetectable at both weeks 4 and 12 received 48 weeks treatment. The primary endpoint was SVR12, defined as an HCV RNA < lower limit of quantification (LLOQ), target detected (TD) or target not detected (TND) at follow-up week 12. A total of 82 patients were randomised to daclatasvir + PR and 42 patients to placebo + PR.

With backward imputation analysis, SVR12 was achieved in 82% (67/82) of patients in the daclatasvir + PR group and 43% (18/42) of patients in the placebo + PR group. At end of treatment, HCV RNA was undetectable in 90% (74/82) of patients in the daclatasvir + PR group and 64% (27/42) of patients in the placebo + PR group. On-treatment virologic failure included virologic breakthrough (confirmed increased in viral load >1 $\log_{10}$ from nadir or any confirmed HCV RNA ≥LLOQ after confirmed undetectable while on treatment), patients who met the protocol-defined treatment futility criteria, and patients with missing or detectable HCV RNA at end of treatment. It occurred in 10% (8/82) of patients in the daclatasvir + PR group and 36% (15/42) of patients in the placebo + PR group. Relapse was defined as confirmed detectable HCV RNA ≥LLOQ during follow-up among patients with HCV undetectable at end of treatment and occurred in two patients in the daclatasvir + PR group and eight patients in the placebo + PR group.

In a phase IIb study (AI444-010), treatment naive CHC patients with genotype 1 and 4 HCV were randomised to treatment with daclatasvir 20mg [not proposed licensed dose and therefore not discussed further] + PR, daclatasvir 60mg + PR (doses as before) for 12 weeks or placebo + PR (doses as before, for 48 weeks). [8,9,11,12] At week 12, patients in the daclatasvir 60mg + PR group who had HCV RNA <LLOQ at week 4 and undetectable at week 10 were then randomised to receive another 12 weeks of daclatasvir 60mg + PR or placebo + PR, for a total treatment duration of 24 weeks. Patients who did not meet these criteria continued PR to week 48. In the subgroup of 18 patients with genotype 4 HCV (relevant to the licensed indication), SVR24 (and SVR12) were achieved in 100% (12/12) of patients treated with daclatasvir + PR and 50% (3/6) of patients treated with placebo + PR.

An on-going, three year, observational, follow-up study (AI444-046) recruited patients who had received at least one dose of daclatasvir (or asunaprevir, an experimental direct acting antiviral [DAA]) and completed the study within the previous six months.[8,9] Patients are to be followed-up at 24 to 48 week intervals. The primary end-point is the time to loss of virologic response after achieving SVR12 in the previous study. Limited data are available; among patients who achieved SVR12 with

daclatasvir and sofosbuvir (± ribavirin) with a median duration of post-SVR12 follow-up of 15 months, no relapses have occurred. Among patients who achieved SVR12 with daclatasvir + PR with a median duration of post-SVR12 follow-up of 22 months, 1% of patients relapsed.

*Other data were also assessed but remain commercially confidential.**

Summary of evidence on comparative safety

In study AI444-040, adverse events (AE) occurring in ≥10% of total population were fatigue (37%), headache (29%), nausea (19%), arthralgia (10%) and diarrhoea (10%). Serious AE occurred in 15 patients: daclatasvir + sofosbuvir + ribavirin for 12 weeks (2.4% [1/41]) and 24 weeks (12% [6/49]); daclatasvir + sofosbuvir for 12 weeks (2.4% [1/41]) and 24 weeks (8.8% [7/80]). Serious AE included single events of gastroenteritis, colitis, cerebrovascular accident, acute renal failure (from dehydration; resolved with fluid administration), forearm fracture, anxiety and pleuritic pain, psoriasis exacerbation, and hypokalaemia. Grade 3/4 AE occurred in seven patients: daclatasvir + sofosbuvir +ribavirin for 12 weeks (2.4% [1/41]) and 24 weeks (6.1% [3/49]); daclatasvir + sofosbuvir for 12 weeks (2.4% [1/41]) and 24 weeks (2.5% [2/80]). The mean change in haemoglobin for ribavirin- versus non-ribavirin-containing regimens in patients treated for 24 weeks was -2.2g/dL versus -0.30g/dL and in patients treated for 12 weeks was -2.8g/dL versus -0.90g/dL. Five patients had their ribavirin dose reduced for anaemia. The EMA noted that daclatasvir + sofosbuvir was well tolerated with low rates of serious AE and discontinuations due to tolerability issues. The addition of ribavirin impacted on the safety profile, with decreases in haemoglobin.

*Other data were also assessed but remain commercially confidential.**

Summary of clinical effectiveness issues

Daclatasvir has been available in Europe for compassionate use since 2013 and received a positive opinion from the EMA, via an accelerated assessment, in June 2014. It may be used in a peginterferon- and ribavirin-free regimen for genotype 1 and 4 HCV, peginterferon-free regimen in genotype 3 HCV and, in genotype 4 HCV, in combination with PR. UK and International guidance recommend the use of triple therapy (a DAA plus PR) for genotype 1 HCV. [13-15] However, there are two other licensed peginterferon-free regimens (sofosbuvir + ribavirin and simeprevir + sofosbuvir ± ribavirin). The daclatasvir peginterferon-free regimen may be used in treatment naive patients and does not require patients to be ineligible or intolerant to peginterferon, unlike the sofosbuvir and simeprevir containing regimens. These regimens are included in recommendations published by the European Association for the Study of the Liver.[16] For genotype 4 HCV, peginterferon-containing comparator regimens include sofosbuvir + PR, simeprevir + PR, or PR alone. While the company submission was for the full licensed indication, after the New Drugs Committee meeting, the company clarified that the submission is focussed on chronic hepatitis C patients who have the most severe disease (METAVIR score ≥ F3, including compensated cirrhosis).

In study AI444-040, across the genotype 1 and 3 subgroups, 89% to 98% achieved SVR12, and 100% of patients with ≥F3 fibrosis achieved SVR12. Most patients were treatment naïve but 41 patients had failed previous treatment with a telaprevir- or boceprevir-containing regimen. The study excluded patients with evidence of cirrhosis or medical conditions associated with chronic liver disease other than HCV. Evidence of efficacy in patients with genotype 3 HCV is limited to data from 18 patients, and for patients with genotype 4 HCV is extrapolated from genotype 1 HCV data. Finally, the value of adding ribavirin to the daclatasvir/sofosbuvir combination remains unclear from this study. In study AI444-042, where patients had treatment naive genotype 4 HCV, a significantly higher proportion of

patients achieved SVR12 in the daclatasvir + PR group than placebo + PR group. SVR12 has been accepted by European and US regulators as an appropriate primary endpoint in clinical studies of treatments for CHC.[17]

In summary, efficacy data are limited to open-label studies, which did not include relevant comparator treatment arms. Comparative efficacy of daclatasvir treatment regimens versus peginterferon-free regimens or a DAA plus PR is not known from head to head studies. Evidence of efficacy of daclatasvir treatment regimens in patients who have received previous treatment is very limited. The EMA noted that the exact magnitude of effect in patients with cirrhosis and advanced liver disease is unknown; however, they considered that the drug combination has the potential of delivering high SVR rates in patients with advanced liver disease.[1]

Due to the limited comparative data, three sources of clinical data were used in the economic analysis included in the company's submission. The first source was the results from a matching adjusted indirect comparison (MAIC) which compared the efficacy and safety of daclatasvir + sofosbuvir ± ribavirin with telaprevir +PR, boceprevir + PR and sofosbuvir + PR in treatment-naive patients with genotype 1 HCV. A MAIC was required due to lack of common comparator arm and used patient level data from the AI444-040 study, matched with aggregate data from the four comparator regimen studies. The key efficacy endpoint was the proportion of patients achieving SVR24 (or 12); daclatasvir + sofosbuvir ± ribavirin was significantly more effective than the comparator regimens for the whole population. Results presented for the subgroup of patients with significant fibrosis (F3/4) are from naïve unadjusted data. In addition to the efficacy end-point, discontinuations due to AE and incidence of AE were also compared. A MAIC in treatment naive patients with genotype 3 HCV was also undertaken using patient level data from AI444-040 study, matched with pooled data from three comparator studies. SVR24 was significantly higher for daclatasvir + sofosbuvir ± ribavirin than the comparator, peginterferon + ribavirin._ The second source of clinical data was a meta-analysis of SVR24 rates in patients treated with: PR (genotypes 1 to 4 HCV), telaprevir + PR (genotype 1 HCV) and boceprevir + PR (genotype 1 HCV). Finally, data from individual studies ("naïve trial data") were also used in the economic analysis.

The availability of daclatasvir will offer another peginterferon-containing treatment option for patients with genotype 4 HCV and another peginterferon-free regimen in patients with genotype 1, 3 and 4 HCV. Clinical experts consulted by SMC considered that daclatasvir is a therapeutic advancement along with other new DAA and considered that its place in therapy is within a peginterferon-free regimen.

Summary of comparative health economic evidence

The submitting company presented cost-utility analyses of daclatasvir in combination with sofosbuvir or PR (ribavarin incorporated where indicated by the licence) against a range of comparator treatments which were dependent on the patient's genotype, previous treatment status and suitability for receiving an interferon-based treatment regimen. Comparators therefore include pegylated interferon + ribavarin, boceprevir + PR, telaprevir + PR, sofosbuvir + ribavarin or + PR. In some cases a no treatment option was also considered. This gave rise to a large number of possible cost-effectiveness ratios to cover all possible scenarios. Comparisons against sofosbuvir-containing regimens may be considered less relevant given that SMC has only recently issued guidance on the medicine but may in the future be considered a relevant alternative.

The economic analyses were conducted over a lifetime horizon. The submitting company presented the analyses for the whole population (F0-F4) but also targeted their submission to the subpopulations

of patients who had significant fibrosis (F3/F4 but were non-cirrhotic) and patients who had compensated cirrhosis on the basis that these are patient groups with the greatest unmet need.

A Markov model was used which included health states covering fibrosis states F0-F4, SVR, hepatocellular carcinoma, decompensated cirrhosis, liver transplant and death. The key variable driving the model's outputs was the rate of SVR achieved by each different regimen and these data were drawn from a range of different sources, including the indirect comparisons discussed above, trial data, naive indirect comparisons and assumptions. The model assumed that patients who achieved an SVR were essentially 'cured' and reverted to baseline population mortality risks. "No treatment" regimens were assumed to have a zero rate of SVR. Progression through the health states in the model were estimated using transition probabilities from literature sources. The model structure, transitions, and the assumptions made around SVRs were similar to those seen in other submissions to SMC for chronic HCV treatments.

Utility values were taken from the published studies. On-treatment disutility was incorporated into model and the gain in utility associated with an SVR was around 0.05 for F0-F3 patients (as per previous submissions) but was 0.17 for patients experiencing an SVR from the F4 state. Costs related to the medicine acquisition cost, monitoring costs and the healthcare management costs associated with progression to the more serious health states in the model and these were estimated from published sources.

Due to the number of treatment alternatives and patient groups, the base case cost effectiveness results ran to almost 100 different incremental cost effectiveness ratios (ICERs) and as such it is not possible to present all of these figures here. Given the focus of the submission to the subgroups of patients with significant fibrosis or compensated cirrhosis, these ICERs are presented below for the different treatment regimens of daclatasvir:

(a) Daclatasvir + sofosbuvir (± ribavirin):

Patients with significant fibrosis (METAVIR score F3–F4)

Population		**comparator**	**Comparator regimen**	**ICER (£/QALY)**
Genotype	**Treatment status**			
1	Naïve	TVR/BOC + PR	No treatment	3,206
			PR	7,982
			TVR + PR	8,157
			BOC + PR	3,021
	Experienced	No treatment	No treatment	3,206
	IFN ineligible/intolerant	No treatment	No treatment	3,206
3	Naïve	PR	No treatment	11,942
			PR	29,589
	Experienced	PR or no treatment	No treatment	11,961
	IFN ineligible/intolerant	No treatment	No treatment	11,961
4	Naïve	PR	No treatment	2,719
			PR	8,102
	Experienced	PR or no treatment	No treatment	2,729
			PR	2,714
	IFN ineligible/intolerant	No treatment	No treatment	2,729

Patients with compensated cirrhosis

Population		comparator	Comparator regimen	ICER (£/QALY)
Genotype	Treatment status			
1	Naïve	TVR/BOC + PR	No treatment	10,042
			PR	19,377
			TVR + PR	25,856
			BOC + PR	20,132
	Experienced	No treatment	No treatment	10,042
	IFN-ineligible/intolerant	No treatment	No treatment	10,042
3	Naïve	PR	No treatment	9,766
			PR	24,819
	Experienced	PR or no treatment	No treatment	10,207
			PR	27,892
4	Naïve	PR	No treatment	10,069
			PR	13,925
	Experienced	PR or no treatment	No treatment	10,069
			PR	11,639
	IFN-ineligible/intolerant	No treatment	No treatment	10,069

(b) Daclatasvir + PR:

Patients with significant fibrosis (METAVIR score F3–F4)

Population		comparator	Comparator regimen	ICER (£/QALY)
Genotype	Treatment status			
4	Naïve	PR	No treatment	3,101
			PR	11,940
	Experienced	PR or no treatment	No treatment	3,101
			PR	3,175

Patients with compensated cirrhosis

Population		Most appropriate comparator*	Comparator regimen	ICER (£/QALY)
Genotype	Treatment status			
4	Naïve	PR	No treatment	2,544
			PR	4,594
	Experienced	PR or no treatment	No treatment	2,544
			PR	2,709

Extensive sensitivity analyses were presented around each of the base case ICERs. These showed that the results were most sensitive to shortening the time horizon and to changes in the SVR inputs. Shortening the time horizon led to ICERs well in excess of £50k in many scenarios but lifetime horizons have been accepted in previous submissions.

The following issues are noted with the analysis:

- There are weaknesses in the clinical data used within the economic model as noted above. Some data are taken from naive indirect comparisons, some from a MAIC which has limitations and some by assumption. In some cases there are small patient numbers at the level of the groups considered. Similar challenges with the clinical data have been seen in other recent submissions. The submitting company did provide sensitivity analysis showing the impact of assuming lower rates of SVRs and threshold analyses showing the values which would result in daclatasvir no longer being cost-effective. The threshold analysis was helpful in showing that fairly substantial falls in the effectiveness of daclatasvir would be necessary to increase the ICERs above conventional levels of cost-effectiveness.
- The utility gain for F4 patients who achieve an SVR was particularly high (0.17) and the company was asked to provide additional analysis assuming a lower gain (0.05) consistent with other submissions. This analysis was helpful in showing that while the ICERs increased by 25% to 50% when this alternative value was used, most of the results remained within acceptable limits of cost-effectiveness
- For some of the patient groups presented, with sofosbuvir regimens as the comparators, the cost-effectiveness ratios were in excess of conventional thresholds but, as noted above, this is not currently the treatment that would be displaced and thus is a less relevant set of comparisons.

Despite the uncertainty with the clinical data underpinning the model, the economic case has been demonstrated for patients with significant fibrosis or compensated cirrhosis.

Summary of patient and public involvement

The following information reflects the views of the specified patient groups.

- Submissions were received from the Hepatitis Scotland (HS), Waverley Care, Haemophilia Scotland and The Hepatitis C Trust (HCT), which are all registered charities.

- All four charities have received funding from pharmaceutical companies in the past two years. HS and HCT have received some funding from the submitting company.

- Hepatitis C is a blood-borne virus that can result in inflammation and significant damage to the liver, affecting the liver's ability to perform its essential functions. Recent research has shown that the hepatitis C virus (HCV) affects a number of other areas of the body including the digestive, lymphatic, immune systems, eyes and the brain.

- People living with the disease can be seriously debilitated and may not be able to work. People have lost their jobs when they have revealed their HCV status. It is also significantly stigmatised. Living with HCV is thus often a challenge with the impact on family and carers as well as the person with the virus.

- Current treatments are lengthy and may have significant side effects that are often difficult to tolerate. Daclatasvir may be more easily tolerated, with shorter treatment duration, fewer hospital visits and a potentially improved side-effect profile.

Additional information: guidelines and protocols

The Scottish Intercollegiate Guidelines Network (SIGN) guideline number 133, management of hepatitis C, was published in July 2013.[13] The following recommendations are included:

- Treatment-naïve and treatment-experienced patients infected with hepatitis C genotype 1 should be considered for treatment with pegylated interferon and weight based ribavirin with the addition of a protease inhibitor as triple therapy.
    - Response-guided therapy can only be used in treatment-naïve patients and previous treatment relapsers who are not cirrhotic.
- For patients with hepatitis C genotype 4 (and 5 or 6) infection, standard treatment should be 48 weeks of pegylated interferon and weight based ribavirin.
- Patients co-infected with HIV and hepatitis C genotype 1 should be considered for treatment with a regimen that includes a hepatitis C virus protease inhibitor.
    - Treatment-naïve patients with HIV and hepatitis C genotype 1 who are unsuitable for this regimen should be considered for treatment with pegylated interferon and weight based ribavirin for 48 to 72 weeks depending on viral response.
    - For patients co-infected with HIV and hepatitis C genotype 1 who do not achieve an early virological response, treatment should be stopped.
    - Patients with HIV and hepatitis C non-genotype 1 who are considered suitable for treatment, should be offered pegylated interferon and weight-based ribavirin for 48 weeks.
- Patients co-infected with hepatitis B and C should be considered for treatment with pegylated interferon and weight-based ribavirin.

The European Association for Study of the Liver (EASL) published EASL Clinical Practice Guidelines: Management of hepatitis C virus infection in 2014.[14] The guidelines includes the following recommendations:

Genotype 1

- The combination of PR and telaprevir or boceprevir is the approved standard of care for chronic hepatitis C genotype 1. There is no head-to-head comparison to allow recommendation of telaprevir or boceprevir as preferred therapy
- Patients with cirrhosis should never receive abbreviated treatment in boceprevir or telaprevir treatment regimens
- Selected patients with high likelihood of SVR to PR or with contraindications to boceprevir or telaprevir can be treated with dual therapy
- When lead-in is used to identify patients with interferon-α- sensitive infection, the possibility of continuation of dual therapy should have been discussed with the patient prior to initiation of treatment
- Both pegylated interferon-α molecules, peginterferon-α 2a(180microgram/week) and peginterferon-α 2b (1.5microgram/kg/week), can be used in dual or triple therapy
- Ribavirin should be dosed following the pegintereron-α label for triple therapy
- Ribavirin should be given at a weight-based dose of 15mg/kg in dual therapy
- Genotype 2, 3, 4, 5 and 6 treatment naive patients
- The combination of peginterferon-α and ribavirin is the approved standard of care for chronic hepatitis C genotype 2, 3, 4 ,5, and 6
- Ribavirin should be given at a weight-based dose of 15mg/kg for genotypes 4, 5, and 6 and at a flat dose of 800mg/day for genotypes 2 and 3
- Patients with genotypes 2 and 3 with baseline factors suggesting low responsiveness should receive weight-based ribavirin at the dose of 15mg/kg

EASL published EASL recommendations on treatment of hepatitis C in April 2014.[16] Detailed guidance on treatment regimens for different genotypes and clinical situations are included. Daclatasvir is recommended for treatment of genotype 1, 3 and 4 CHC.

The World Health Organisation (WHO) published Guidelines for the screening, care and treatment of persons with hepatitis C infection in April 2014.[15]
The guidelines include the following recommendations for treatment:

- Pegylated interferon in combination with ribavirin is recommended for the treatment of chronic HCV infection rather than standard non-pegylated interferon with ribavirin.
- Treatment with telaprevir or boceprevir, given in combination with pegylated interferon and ribavirin, is suggested for genotype 1 chronic hepatitis C infection rather than pegylated interferon and ribavirin alone.
- Sofosbuvir, given in combination with ribavirin with or without pegylated interferon (depending on the HCV genotype), is recommended in genotypes 1, 2, 3 and 4 HCV infection rather than pegylated interferon and ribavirin alone (or no treatment for persons who cannot tolerate interferon).

Additional information: comparators

Peginterferon-free comparator regimens are sofosbuvir plus ribavirin or simeprevir plus sofosbuvir ± ribavirin. Other antiviral + PR for genotype 1 CHC include telaprevir + PR and boceprevir + PR. For patients with genotype 4 CHC, treatment is with sofosbuvir + PR, simeprevir + PR or PR alone.

Cost of relevant comparators

Drug	Dose Regimen	Cost per year (£)
Peginterferon-free regimens*		
daclatasvir sofosbuvir	**60mg orally daily for 12 to 24 weeks** **400mg orally daily 12 to 24 weeks****	**59,502 to 119,004**
daclatasvir sofosbuvir ribavirin	**60mg orally daily for 24 weeks 400mg orally daily for 24 weeks 1000mg to 1,200mg orally daily for 24 weeks**	**120,852**
simeprevir sofosbuvir ± ribavirin	150mg orally daily for 12 weeks 400mg orally daily for 12 weeks 1000mg to 1200mg orally daily for 12 weeks	57,381 to 58,306
sofosbuvir ribavirin	400mg orally daily for 24 weeks 1000mg to 1200mg orally daily for 24 weeks	71,816
Peginterferon containing regimens^		
daclatasvir peginterferon-alfa-2a ribavirin	**60mg orally daily for 24 weeks 180 micrograms sc once weekly 24 to 48 weeks 1000mg to 1200mg orally daily for 24 to 48 weeks**	**53,872 to 58,707**
simeprevir peginterferon-alfa-2a ribavirin	150mg orally daily for 12 weeks 180 micrograms sc once weekly for 24 to 48 weeks 1000mg to 1200mg orally daily for 24 to 48 weeks	27,234 to 32,069
sofosbuvir peginterferon-alfa-2a ribavirin	400mg orally daily for 12 to 24 weeks 180 micrograms sc once weekly for 12 to 24 weeks 1000mg to 1200mg orally daily for 12 to 24 weeks	37,401 to 74,802
boceprevir peginterferon-alfa-2b	800mg three times daily for 24 to 48 weeks 1.5mcg/kg once weekly for 28 to 48 weeks	22,397 to 43,194

ribavirin	800mg to 1800mg orally daily for 28 to 48 weeks	
telaprevir peginterferon-alfa-2a ribavirin	2250mg daily in divided doses for 12 weeks 180mcg sc once weekly for 24 to 48 weeks 1000mg to 1200mg orally daily for 24 to 48 weeks	27,234 to 32,069
peginterferon-alfa-2a ribavirin	180 micrograms sc once weekly for 24 to 48 weeks 1000mg to 1200mg orally daily for 24 to 48 weeks	4,836 to 9,671
peginterferon-alfa-2b ribavirin	1.5microgram/kg sc once weekly for 24 to 48 weeks 800mg to 1800mg daily for 24 to 48 weeks	4,797 to 9,594

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis (July 2014), MIMS and company's submission (daclatasvir). Costs are based on a body weight of 70kg (ribavirin dose of 1,000mg/day). sc=subcutaneously

*for peginterferon-free regimens; daclatasvir is licensed for genotype 1 and 4 (without ribavirin) and genotype 3 (with ribavirin), simeprevir for genotype 1 and 4, sofosbuvir for genotype 1-6 HCV.

**12 weeks without cirrhosis and 24 weeks with compensated cirrhosis

^for peginterferon containing regimens; daclatasvir is licensed for genotype 4, simeprevir for genotype 1 and 4, sofosbuvir for genotype 1,3,4,5 and 6, boceprevir and telaprevir for genotype 1 HCV.

Additional information: budget impact

The submitting company has provided a budget impact template only for the subgroup of F3/F4 patients (all genotypes).

The submitting company estimated there to be 37600 patients with hepatitis C, of whom 1034 patients per year receive treatment. The company estimated that 23.6% of these patients would then be eligible for treatment with daclatasvir (F3/F4 only) i.e. 244 patients per year with an estimated uptake rate of 13% and 50% in years 1 and 5 respectively to result in 32 patients being treated in year 1 rising to 122 in year 5.

The submitting company estimated the gross medicines budget impact to be £3.01m in year 1 and £11.58m in year 5. As other medicines were assumed to be displaced, the net medicines budget impact was estimated to be £2.39m in year 1 and £9.12m in year 5.

These figures assume that 30% of patients receive 12 week regimens of daclatasvir + sofosbuvir, 18% receive 24 weeks of daclatasvir + sofosbuvir and 46% receive 24 weeks of daclatasvir + sofosbuvir + ribavarin. In terms of displaced treatments, the company has assumed that 59% of the displaced medicines cost is from pegylated interferon + ribavarin, 28% from telaprevir and boceprevir regimens, and 12% from use of sofosbuvir regimens.

References

The undernoted references were supplied with the submission. The reference shaded in grey is additional to those supplied with the submission.

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6. Merck Sharp and Dohme. Summary of product characteristics for Victrelis (boceprevir)

7. Sulkowski MS, Gardiner DF, Rodriguez-Torres M, et al. Daclatasvir plus sofosbuvir for previously treated or untreated chronic HCV infection. New England Journal of Medicine. 2014;370(3):211-21.

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9. Bristol Myers Squibb. Summary of product characteristics for daclatasvir (Daklinza) [DRAFT]

10. *Commercial in Confidence*

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14. European Association for Study of the Liver. EASL Clinical Practice Guidelines: Management of hepatitis C virus infection. Journal of Hepatology. 2014: 60; 392-420

15. WHO. Guidelines for the screening, care and treatment of persons with hepatitis C infection, April 2014. http://apps.who.int/iris/bitstream/10665/111747/1/9789241548755_eng.pdf?ua=1&ua=1

16. European Association for the Study of the Liver. EASL recommendations on treatment of hepatitis C. April 2014.

17. European Medicines Agency. European Public Assessment Report for Sovaldi (sofusbuvir). 21 November 2013. EMA/CHMP/688774/2013

This assessment is based on data submitted by the applicant company up to and including 11 September 2014.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/About_SMC/Policy_Statements/Policy_Statements*

Drug prices are those available at the time the papers were issued to SMC for consideration. 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.