Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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elbasvir 50 mg, grazoprevir 100mg film-coated tablet (Zepatier®)

SMC No. (1203/17)

Merck Sharp and Dohme Ltd

09 December 2016

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

elbasvir-grazoprevir (Zepatier®) is accepted for use within NHS Scotland.

Indication under review: Treatment of chronic hepatitis C (CHC) in adults. (The efficacy of elbasvir-grazoprevir has not been demonstrated in genotypes 2, 3, 5 and 6. Elbasvir-grazoprevir is not recommended in patients infected with these genotypes).

In patients with genotype 1a, 1b or 4, elbasvir-grazoprevir significantly increased sustained virologic suppression compared with a regimen containing a non-structural protein 5B (NS5B) inhibitor, an interferon and ribavirin.

This SMC advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost-effectiveness of elbasvir-grazoprevir. This advice is contingent upon the continuing availability of the PAS in NHS Scotland or a list price that is equivalent or lower.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Published 16 January 2017

Indication

Treatment of chronic hepatitis C (CHC) in adults.

Dosing Information

One tablet swallowed whole once daily. In patients with genotype 1a, 1b or 4 who have no cirrhosis or who have Child-Pugh A compensated cirrhosis, treatment should be continued for 12 weeks.

Treatment for 16 weeks plus ribavirin should be considered in patients with genotype 1a or 4, who also have HCV RNA >800,000IU/ml and in patients with genotype 1a who also have specific non-structural protein, NS5A, polymorphisms causing at least a 5-fold reduction in activity of elbasvir to minimize the risk of treatment failure. The ribavirin daily dose should be weight-based (<66kg = 800mg, 66 to 80kg = 1,000mg, 81 to 105kg = 1,200mg and >105kg = 1,400mg, administered in two divided doses with food).

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

The efficacy of elbasvir-grazoprevir has not been demonstrated in HCV genotypes 2, 3, 5 and 6. Elbasvir-grazoprevir is not recommended in patients infected with these genotypes.

Product availability date

November 2016

Summary of evidence on comparative efficacy

Elbasvir-grazoprevir is a fixed dose combination of the non-structural protein 5A (NS5A) inhibitor, elbasvir, and the NS3/4A protease inhibitor, grazoprevir. It is licensed for treatment of chronic hepatitis C virus (HCV) infection in adults. The summary of product characteristics provides dosing information for genotype (GT) 1 and 4 infected patients and notes that it is not recommended for use in patients with GT 2, 3, 5 or 6.[1]

In an open-label phase III study (C-EDGE-H2H), 255 treatment-naive and treatment-experienced adults with GT1 or 4 chronic HCV infection were randomised equally, with stratification by GT (1a or non-1a) and cirrhosis (presence or absence), to oral elbasvir 50mg, grazoprevir 100mg fixed-dose combination tablet once daily or sofosbuvir 400mg once daily plus ribavirin twice daily (weight-based daily dose of 1,000mg to 1,200mg) plus subcutaneous (SC) peg-interferon 1.5microgram/kg once a week for 12 weeks. The primary outcome was sustained virologic response, defined as HCV RNA below limit of quantification (15IU/mL), 12 weeks after the end of treatment (SVR12). A non-inferiority margin of 10% was used to compare elbasvir-grazoprevir with sofosbuvir, peg-interferon plus ribavirin in the full analysis set (FAS), which comprised all randomised patients who received at least one dose of study treatment. Elbasvir-grazoprevir significantly increased SVR12 compared with the comparator regimen: 99.2% (128/129) versus 91.5% (114/126). Subgroup analyses are as detailed in table 1.[2]

Two double-blind placebo-controlled (C-EDGE-TN and C-EDGE-COSTAR) and two open-label uncontrolled (C-EDGE-TE and C-EDGE-COINFECTION) phase III studies recruited adults with chronic HCV infection GT1, 4 or 6 who were treatment-naive, except in C-EDGE-TE, where they had failed peg-interferon plus ribavirin. In C-EDGE-COSTAR patients were opiate-dependent and in C-EDGE-COINFECTION patients had HIV infection. Data from treatment-naive and treatment-experienced patients are also available from a double-blind placebo-controlled phase II/III study (C-SURFER) that recruited adults with GT1 and chronic kidney disease and from two open-label uncontrolled phase II studies that recruited adults with GT1 or 3 (C-WORTHY) and GT4 or 6 (C-SCAPE). In all but two of the studies patients who received active treatment were given oral elbasvir 50mg, grazoprevir 100mg once daily for 12 weeks. In the C-EDGE-TE study patients were randomised equally to elbasvir 50mg, grazoprevir 100mg once daily for 12 or 16 weeks or these regimens in combination with weight-based ribavirin twice daily. In C-WORTHY a variety of regimens were investigated. SVR12 was the primary outcome in all studies and results are detailed in table 1 for individual studies and for pooled analyses that included data from relevant subgroups across all the studies.[3-15]

Table 1: Percentage (n/N) SVR12 rates in phase III studies[2-15]

	HCV Genotype (GT) Subgroups			Total population	
	GT1a	**GT1b**	**GT4**	**No Cirrhosis**	**Cirrhosis**
C-EDGE-H2H					
E-G 12wks	100 (18/18)	99 (104/105)	100 (6/6)	99 (106/107)	100 (22/22)
SOF-PEG-R	100 (17/17)	90 (94/104)	60 (3/5)	93 (98/105)	76 (16/21)
C-EDGE-TN					
E-G 12wks	92 (144/157)	99 (129/131)	100 (18/18)	94 (231/246)	97 (68/70)
C-EDGE-TE					
E-G 12wks	90 (55/61)	100 (34/34)	78 (7/9)	94 (64/68)	89 (33/37)
E-G + R 12wks	93 (56/60)	97 (28/29)	93 (14/15)	97 (67/69)	89 (31/35)
E-G 16wks	94 (45/48)	96 (46/48)	60 (3/5)	93 (62/67)	92 (35/38)
E-G + R 16wks	95 (55/58)	100 (36/36)	100 (8/8)	96 (66/69)	100 (37/37)
C-EDGE-COINFECTION					
E-G 12wks	94 (136/144)	95 (42/44)	96 (27/28)	94 (172/183)	100 (35/35)
C-SURFER					
E-G 12wks	100 (61/61)	98 (54/55)		99 (109/110)	100 (6/6)
POOLED (data from phase II data and III studies)*					
E-G 12wks	93 (483/519)	96 (301/312)	94 (61/65)		
E-G + R 16wks	95 (55/58)	-	100 (8/8)		

E-G = elbasvir-grazoprevir; R = ribavirin; SOF= sofosbuvir; PEG = peg-interferon wks = weeks;
* data from the phase III C-EDGE-TN, C-EDGE-COINFECTION, C-EDGE-TE and C-SURFER studies plus the phase II study, C-WORTHY in GT1 analyses and from the phase III C-EDGE TN and C-EDGE-COINFECTION studies plus the phase II study, C-SCAPE, in GT4 analyses.

Analyses were conducted within the resistance analysis population (RAP), which comprised patients from phase II and III studies (C-EDGE-TN, C-EDGE-COINFECTION, C-EDGE-TE, C-SURFER and C-WORTHY) who had achieved SVR12 or had virologic failure and for whom baseline sequencing data was available (i.e. excluded patients who had discontinued the study for reasons other than virologic failure). These indicated that elbasvir-grazoprevir for 12 weeks produced SVR12 in 97% (464/476) of GT1a infected patients without baseline NS5A resistance associated variants and in 53% (16/30) of those with these mutations, with corresponding figures of 99% (259/260) and 92% (36/39) in GT1b infected patients. In GT1a infected patients combining elbasvir-grazoprevir with ribavirin and extending treatment to 16 weeks produced

SVR12 in 100% (51/51) of patients without baseline NS5A resistance associated variants and in 100% (4/4) of those with mutations.[1,3]

Within GT1a infected patients of the RAP population, SVR12 with 12-weeks elbasvir-grazoprevir was achieved by 98% (135/138) of those with baseline viral load less than 800,000units/mL and 91% (348/381) of those with a higher baseline viral load. Corresponding figures for 16-weeks elbasvir-grazoprevir combined with ribavirin were 100% (9/9) and 94% (46/49) in the respective subgroups. The effect of viral load was less apparent in GT1b infected patients, with 12-weeks elbasvir-grazoprevir producing SVR12 in 99% (106/107) and 98% (189/192) of patients with baseline viral load below and above 800,000units/mL, respectively.[1,3]

An open-label phase II study (C-SALVAGE) recruited 79 adults with chronic HCV GT1 who had not achieved SVR after at least four weeks of treatment with a regimen containing peg-interferon, ribavirin plus a protease inhibitor, such as boceprevir, telaprevir or simeprevir. Patients received the unlicensed regimen of elbasvir 50mg and grazoprevir 100mg once daily plus weight-based ribavirin twice daily for 12 weeks. The primary outcome of SVR12 was achieved by 96% (76/79).[16]

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

Summary of evidence on comparative safety

The EMA noted that a pooled analysis of data from C-EDGE-TN, C-EDGE-COINFECTION and C-EDGE-TE indicated that the adverse event profile of elbasvir-grazoprevir was comparable to placebo, whereas the elbasvir-grazoprevir plus ribavirin regimen was associated with increased adverse events: 70% (448/639), 69% (72/105) and 82% (85/104), respectively, which were treatment-related in 36% (230/639), 39% (41/105) and 64% (67/104). Higher rates of drug-related adverse events in the latter group were particularly noted for anaemia, nausea, fatigue, dyspnoea and pruritus. Most drug-related adverse events were mild to moderate in severity. Rates of serious adverse events and discontinuations due to adverse events were low and comparable across the groups.[3]

In the active-controlled study, C-EDGE-H2H, adverse events were reported by fewer patients in the elbasvir-grazoprevir group, compared with the sofosbuvir, peg-interferon, ribavirin group: 52% (67/129) versus 93% (117/126), which were treatment-related in 90% (114/126) versus 25% (32/129) and resulted in discontinuation of study treatment in zero and one patient in the respective groups. Serious adverse events were uncommon: 0.8% (1/129) versus 4.0% (5/126), respectively. Adverse events reported by at least 10% of patients were headache in the elbasvir-grazoprevir group and included pyrexia, headache, fatigue, asthenia, influenza-like illness, chills, myalgia, decreased appetite, anaemia, nausea and cough in the sofosbuvir, peg-interferon plus ribavirin group.[2]

In the three double-blind placebo-controlled studies (C-EDGE-TN, C-EDGE-COSTAR and C-SURFER) there were similar rates of adverse events in the active and placebo groups: 67% versus 69%; 83% versus 83%; and 76% versus 84%, in the respective studies. These were treatment-related in 36% versus 39%; 41% versus 34%; 34% versus 34%, were serious in 2.8% versus 2.9%; 3.5% versus 4.0%; 13% versus 14% and resulted in treatment discontinuation in 0.9% versus 1.0%; 0.5% versus 1.0%; 0 versus 4.4%, in the respective studies.[5,7,13]

During the clinical study programme, late elevations of alanine transaminase (ALT) and aspartate transaminase (AST) were noted to be related to grazoprevir exposure and generally occurred after eight weeks of treatment. Most were short-lived and all resolved. However, there is currently no clear explanation of why they occur at this stage in treatment. At the marketed dose of 100mg grazoprevir, they occurred in less than 1% of patients.[3]

Summary of clinical effectiveness issues

Elbasvir-grazoprevir is the second regimen containing an NS5A and NS3/4A inhibitor for HCV infection. The first was the NS5A inhibitor, ombitasvir, and the NS3/4A inhibitor, paritaprevir, formulated in a fixed-dose combination product, which is licensed in combination with the NS5B inhibitor, dasabuvir, ± ribavirin for treatment of GT1, and in combination with ribavirin for GT4. Two other interferon-free regimens of direct acting antivirals (DAA) licensed for GT1 and GT4 are (1) the NS5A inhibitor, daclatasvir, in combination with the NS5B inhibitor, sofosbuvir, ± ribavirin; and (2) sofosbuvir, plus the NS5A inhibitor, ledipasvir fixed-dose formulation ± ribavirin.[17-20] These regimens are recommended in the national clinical guideline.[21]

In a phase III study, elbasvir-grazoprevir was significantly superior to sofosbuvir, peg-interferon plus ribavirin for SVR12, which is recommended by the EMA as the primary outcome in studies assessing cure rate of HCV.[2,21,22] Elbasvir-grazoprevir was associated with high SVR12 rates across several placebo-controlled and uncontrolled phase II and III studies, which recruited mainly treatment-naive patients. An important factor influencing viral suppression was the presence of NS5A resistance-associated variants and to a lesser extent high viral load (>800,000units/mL) at baseline. The impact of these was greater in patients infected with GT1a than GT1b.[3-15]

The evidence base for elbasvir-grazoprevir derives from studies that recruited mainly treatment-naive patients, with only the C-EDGE-TE and C-SALVAGE studies providing data in treatment-experienced patients. All of the studies excluded patients with chronic hepatitis B virus (HBV) infection and this limits the application of results, especially safety data, to this patient group.[3-15]

There were no direct comparative data for elbasvir-grazoprevir relative to the DAA regimens recommended in the national clinical guideline for treatment of HCV infection and indirect comparisons were presented to address this. These were performed using a naive method and a Bayesian network meta-analysis (NMA) in which imputing of data to permit formation of networks from studies that could not be otherwise linked, was a significant limitation. SVR and safety outcomes were assessed. The indirect comparison of SVR between elbasvir-grazoprevir and the comparator recommended first-line in the national clinical guideline for all GT1 subgroups, ombitasvir-paritaprevir-ritonavir, dasabuvir ± ribavirin, was supported by the most robust data. The data supporting the indirect comparisons of SVR for the alternative regimens (ledipasvir-sofosbuvir and daclatasvir plus sofosbuvir) had more limitations, including use of identical data from mixed genotype populations across analyses in GT1a, GT1b and GT4, and use of unlicensed regimens instead of recommended regimens containing ribavirin in patients with cirrhosis. In addition, there were a number of weaknesses across all the indirect comparisons, including heterogeneity in study design, definitions of treatment-experienced groups and some baseline characteristics. Also, data were generally derived from subgroups that had limited sample size, particularly for GT4 and patients with cirrhosis, and a lack of data on subgroup baseline characteristics limited assessment of heterogeneity. There was also an absence of data on factors that may influence efficacy, such as resistance-associated variants.

The limitations of the indirect comparisons should be viewed in the context of the development process of the national clinical guideline. This notes that within GT1, recent advances in DAA have resulted in regimens close to the ceiling of efficacy with rates of 97% to 100% and that systematic reviews have indicated that several regimens crossed the 90% threshold for efficacy (recommended by the HCV Treatment and Therapies Subgroup of the National Sexual Health and BBV Advisory Committee as the expectation of cure with initial treatment of HCV) and can be regarded as equally efficacious.[21]

Clinical experts consulted by SMC considered that the place in therapy of elbasvir-grazoprevir is as an alternative to interferon-free DAA regimens currently used for treatment of patients with chronic HCV GT1 or GT4 infection.

Summary of comparative health economic evidence

The submitting company presented a cost-minimisation analysis comparing elbasvir-grazoprevir (EBR/GZR) against a range of different comparators according the patient's genotype, cirrhosis status and previous treatment- experience, as shown in table 2 below:

Table 2: Comparators according to patient group

Genotype 1a/1b	Genotype 4
ombitasvir/ paritaprevir/ritonavir+dasabuvir (3D regimen) for 12 weeks for all patients regardless of cirrhosis status or previous treatment experience	ombitasvir/ paritaprevir/ ritonavir (2D regimen) for 12 weeks
Ledipasvir/sofosbuvir (LDV/SOF) for 8 or 12 weeks depending on cirrhosis status or treatment experience	LDV/SOF for 12 weeks
Daclatasvir/ sofosbuvir (DCV/SOF) for 12 weeks for treatment- naive and treatment-experienced non-cirrhotic patients.	DCV/SOF for 12 weeks for treatment-naive and treatment- experienced non-cirrhotic patients

The time horizon of the analysis was that of a single course of treatment, and thus varied between 8 weeks and 16 weeks depending on the regimen being evaluated.

The results of the NMA were used to support the equivalent efficacy of treatments, as is necessary for cost-minimisation analysis to be appropriate. As such, all treatments were assumed to be equivalent in terms of SVRs and adverse events.

Costs in the model related to the medicines acquisition costs of the regimens, plus costs associated with initial evaluation of the patient and ongoing monitoring during treatment. The initial evaluation cost was higher for cirrhotic patients than non-cirrhotic patients but ongoing weekly monitoring costs did not vary by cirrhotic status. No costs were included for any polymorphism tests that may be associated with elbasvir-grazoprevir treatment.

The results of the cost-minimisation analysis for the various patient groups and comparator regimens are presented in table 3.

Table 3: Total costs by regimen and patient group

		Genotype 1a/1b				Genotype 4			
	Duration (wks)	Treatment naïve		Treatment experienced		Treatment naive		Treatment experienced	
		Cirrhotic	Non cirrhotic	Cirrhotic	Non cirrhotic	Cirrhotic	Non cirrhotic	Cirrhotic	Non cirrhotic
EBR/ GZR	12	£38,965	£38,768	£38,126	£38,125	£38,965	£38,768	£38,126	£38,125
	16	£51,255	£51,059	£50,416	£50,416	£51,255	£51,059	£50,416	£50,416
2D	12	N/A	N/A	N/A	N/A	N/A	£34,468	N/A	£33,825
3D	12	£37,465	£37,268	£36,626	£36,625	N/A	N/A	N/A	N/A
LDV/ SOF	8	N/A	£28,130	N/A	N/A	N/A	N/A	N/A	N/A
	12	£41,445	N/A	£40,606	£40,605	£41,445	£41,248	£40,606	£40,605
DCV+SOF	12	N/A	£61,769	N/A	£61,126	N/A	£61,769	N/A	£61,126

A patient access scheme (PAS) was submitted by the company and was assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland. Under the PAS, a simple discount was offered on the price of the medicine. With the PAS, elbasvir-grazoprevir became a cost-effective treatment option.

SMC would wish to present the with-PAS cost-effectiveness estimates that informed the SMC decision. However, owing to the commercial in confidence concerns regarding the PAS, SMC is unable to publish these results. As such, only the without-PAS figures can be presented.

Given the simplicity of the analysis, no sensitivity analysis was provided.

The analysis was associated with a number of weaknesses or uncertainties:

- The key weakness is that the cost-minimisation analysis rests on the conclusions of the indirect comparisons, which are associated with a number of weaknesses as noted above. In particular, there are concerns around the use of imputation in the NMA.
- The analysis does not include the costs of any testing associated with polymorphism; however, the company has indicated that the cost of the test is likely to be in the region of £85 to £100 and thus would not affect the results of the analysis.
- The analysis uses shorter treatment durations for the comparator regimens, which are consistent with clinical guidelines used in NHS Scotland, but which may be shorter than those which formed the basis of SMC advice. However, this does not result in bias in favour of elbasvir-grazoprevir.
- A simplifying assumption has been made to exclude the costs of ribavirin, which may be used with a number of the treatment regimens. However, this is not likely to be a source of bias.

Despite the weakness with the comparative evidence base underpinning the cost-minimisation analysis, the economic case has been demonstrated.

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

Summary of patient and public involvement

The following information reflects the views of the specified Patient Groups:

- We received patient group submissions from Hepatitis C Trust, Hepatitis Scotland and Waverley Care.

- The Hepatitis C Trust has received 50% pharmaceutical company funding in the past two years, including from the submitting company. Hepatitis Scotland has received 0.85% pharmaceutical company funding in the past two years, but none from the submitting company. Waverley Care has received 1.7% pharmaceutical company funding in the past two years, but none from the submitting company.

- Hepatitis C is a blood-borne virus that predominantly infects liver cells. This can result in inflammation and significant damage to the liver. The resultant damage can cause very debilitating symptoms, including cirrhosis, liver cancer and liver failure. It is a significantly stigmatised disease that can affect employability. All these factors mean that it has a devastating impact on the patients, their family and carers.

- Hepatitis C is curable but therapies vary in effectiveness and tolerability. Current treatment regimens can be lengthy (up to 24 weeks) and interferon-containing treatment regimens in particular have significant side-effects and not all patients can tolerate them.

- Elbasvir-grazoprevir offers an effective treatment for Hepatitis C. It is an oral therapy with a shorter treatment time and a tolerable side-effect profile compared to current treatments. There is less need for frequent hospital visits and a reduced number of blood tests during treatment, which enables patients to be treated without a significant disruption to their working and family lives.

Additional information: guidelines and protocols

In December 2015 Healthcare Improvement Scotland and NHS National Services Scotland published National Clinical Guideline for the treatment of HCV in adults, version 2.0. For GT1 infected patients without cirrhosis they recommend first-line treatment with 12-weeks ombitasvir-paritaprevir-ritonavir, dasabuvir ± ribavirin (with sofosbuvir-ledipasvir for 8 weeks, sofosbuvir plus simeprevir for 12 weeks and sofosbuvir plus daclatasvir for 12 weeks as alternatives in those who are treatment-naïve; and 12 week courses of sofosbuvir-ledipasvir or sofosbuvir plus daclatasvir in those who are treatment-experienced). Ombitasvir-paritaprevir-ritonavir, dasabuvir plus ribavirin for 12 weeks is recommended as the first-line treatment for patients with cirrhosis (with 12 weeks courses of sofosbuvir-ledipasvir plus ribavirin or sofosbuvir, daclatasvir plus ribavirin as alternative regimens). The guideline notes that GT4 is uncommon in Scotland and treatment should be in accordance with local protocols or on the basis of expert advice.[21]

In July 2013 the Scottish Intercollegiate Guidelines Network (SIGN) issued publication number 133: management of hepatitis C. The guideline pre-date the availability of interferon-free DAA regimens.[24]

In February 2016 the British Society of Gastroenterology published consensus treatment recommendations for management of patients with chronic HCV infection. This recommends for patients without cirrhosis 12 weeks of ombitasvir-paritaprevir-ritonavir, dasabuvir plus ribavirin for those with GT1a, 12-weeks ombitasvir-paritaprevir-ritonavir plus dasabuvir for those with GT1b or for patients with GT1 (a or b) sofosbuvir-ledipasvir for 8 weeks in treatment-naive patients and for 12 weeks in treatment-experienced patients. In patients with cirrhosis 12 weeks sofosbuvir-ledipasvir ± ribavirin or 12-weeks ombitasvir-paritaprevir-ritonavir, dasabuvir plus ribavirin are options, with 24 weeks of the latter regimen also an option in treatment-experienced patients.[25]

Additional information: comparators

A variety of DAA regimens are licensed for treatment of GT1 and GT4 chronic HCV and these are detailed in the table below. The national guideline[21] provides recommendations on appropriate treatments for individual patients based on previous treatment and presence of cirrhosis. These are summarised above.

Cost of relevant comparators

Drug	Dose Regimen	Cost per course (£)
Elbasvir-grazoprevir Ribavirin	**One tablet daily for 16 weeks 1,000 to 1,400mg daily for 16 weeks**	**49,739 to 50,167**
Elbasvir-grazoprevir	**One tablet daily for 12 weeks**	**36,500**
Ombitasvir-paritaprevir-ritonavir Dasabuvir Ribavirin	Two tablets once daily for 24 weeks One tablet twice daily for 24 weeks 1,000 to 1,200mg daily for 24 weeks	71,607 to 71,929
Ombitasvir-paritaprevir-ritonavir Dasabuvir Ribavirin	Two tablets once daily for 12 weeks One tablet twice daily for 12 weeks 1,000 to 1,200mg daily for 12 weeks	35,804 to 35,965
Ombitasvir-paritaprevir-ritonavir Dasabuvir	Two tablets once daily for 12 weeks One tablet twice daily for 12 weeks	35,000
Ombitasvir-paritaprevir-ritonavir Ribavirin	Two tablets once daily for 12 weeks 1,000 to 1,200mg daily for 12 weeks	33,004 to 33,165
Ledipasvir-sofosbuvir	One tablet daily for 24 weeks	77,960
Ledipasvir-sofosbuvir Ribavirin	One tablet daily for 12 weeks 1,000 to 1,400mg daily for 12 weeks	39,784 to 40,105
Ledipasvir-sofosbuvir	One tablet daily for 12 weeks	38,980
Ledipasvir-sofosbuvir	One tablet daily for 8 weeks	25,987
Daclatasvir Sofosbuvir Ribavirin	60mg orally once daily for 24 weeks 400mg orally once daily for 24 weeks 1,000 to 1,400mg daily for 24 weeks	120,608 to 121,251

Daclatasvir Sofosbuvir	60mg orally once daily for 24 weeks 400mg orally once daily for 24 weeks	119,001
Daclatasvir Sofosbuvir Ribavirin	60mg orally once daily for 12 weeks 400mg orally once daily for 12 weeks 1,000 to 1,400mg daily for 12 weeks	60,304 to 60,626
Daclatasvir Sofosbuvir	60mg orally once daily for 12 weeks 400mg orally once daily for 12 weeks	59,501

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 3 September 2016. Cost of elbasvir-grazoprevir from company submission. Costs do not take any patient access schemes into consideration.

Additional information: budget impact

The company estimated there would be 735 patients eligible for treatment with elbasvir-grazoprevir in all years. This estimate related to genotype 1 patients only. The uptake rate was estimated to be 100% in all years.

SMC is unable to publish the with-PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS.

References

The undernoted references were supplied with the submission.

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This assessment is based on data submitted by the applicant company up to and including 08 November 2016.

**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 technologyappraisal: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.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a drug and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG, established under the auspices of NHS National Services Scotland reviews and advises NHS Scotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHS Scotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

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.