NICE National Institute for Health and Care Excellence

NICE guidance

Glecaprevir–pibrentasvir for treating chronic hepatitis C

Technology appraisal guidance
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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

1 Recommendations

1.1 Glecaprevir–pibrentasvir is recommended, within its marketing authorisation, as an option for treating chronic hepatitis C in adults, only if the company provides the drug at the same price or lower than that agreed with the Commercial Medicines Unit.

1.2 It is recommended that the decision to treat and prescribing decisions are made by multidisciplinary teams in the operational delivery networks put in place by NHS England, to prioritise treatment for people with the highest unmet clinical need.

Why the committee made these recommendations

Current treatment options for chronic hepatitis C depend on genotype, cirrhosis status and treatment history. Glecaprevir–pibrentasvir is suitable for all genotypes and has a shorter treatment duration than most other direct-acting antiviral treatments.

Clinical trials show that glecaprevir–pibrentasvir is effective for treating chronic hepatitis C across all genotypes. There was only 1 trial directly comparing glecaprevir–pibrentasvir with other direct-acting antiviral regimens, but comparing individual arms of clinical trials of other direct-acting antivirals suggests that glecaprevir–pibrentasvir works as well as most direct-acting antiviral drugs that NICE already recommends for treating hepatitis C.

The analysis shows that cost-effectiveness estimates for glecaprevir–pibrentasvir across all populations are substantially below what NICE usually considers acceptable. It is therefore recommended for treating chronic hepatitis C.

2 Information about glecaprevir–pibrentasvir

Marketing authorisation

2.1 Glecaprevir–pibrentasvir (Maviret, AbbVie) has a marketing authorisation in the UK for the 'treatment of chronic hepatitis C virus infection in adults'. This includes genotypes 1–6, with or without compensated cirrhosis, in people with untreated disease or disease previously treated with interferon-based treatment or sofosbuvir plus ribavirin. It is not approved for people whose previous treatment included a NS3/4A and/or NS5A inhibitor.

Dosage in the marketing authorisation

2.2 The dosage is 300 mg/120 mg orally once daily. Treatment duration is 8, 12 or 16 weeks depending on genotype, cirrhosis status and whether the person has had previous treatment.

Price

2.3 The list price per pack is £12,993.66. The total costs are £25,987.32 for an 8-week course, £38,980.98 for 12 weeks and £51,974.64 for 16 weeks. The company has agreed a nationally available price reduction for glecaprevir–pibrentasvir with the Commercial Medicines Unit. The contract prices agreed through the framework are commercial in confidence.

3 Committee discussion

The appraisal committee (section 5) considered evidence submitted by AbbVie and a review of this submission by the evidence review group (ERG). See the committee papers for full details of the evidence.

Clinical management

People with hepatitis C would welcome an additional treatment option that is suitable for all genotypes and free from peginterferon

3.1 The use of interferon-based treatments has reduced substantially in clinical practice because of the introduction of newer direct-acting antivirals for all hepatitis C virus (HCV) genotypes, with the exception of genotype 2. Clinical and patient experts stated that glecaprevir–pibrentasvir is an important treatment because it is effective in all genotypes, which reduces the need for baseline genotype testing and could improve access to treatment. Unlike sofosbuvir-based regimens, glecaprevir–pibrentasvir is suitable for people with severe renal impairment. This is particularly important for genotypes 2, 3, 5 and 6 in which the only interferon-free treatments available have a sofosbuvir component. In addition to being free from interferon, ribavirin and sofosbuvir, glecaprevir–pibrentasvir has a short treatment duration of 8 weeks for disease without cirrhosis for most HCV genotypes. The committee recognised that patients and clinicians would welcome an additional effective and tolerable treatment for all HCV genotypes and concluded that glecaprevir–pibrentasvir is a valuable treatment option.

The relevant comparators are included

3.2 The company did not include some of the comparators listed in the NICE scope, noting that they are no longer used in clinical practice:

- daclatasvir plus sofosbuvir for genotypes 1 and 4

- peginterferon alfa plus ribavirin for all genotypes (except genotype 2, in people who are treatment naive, without cirrhosis, and who are eligible for treatment with interferon)
- sofosbuvir plus with ribavirin for genotypes 1 and 4.

  The clinical experts confirmed that these comparators are rarely used in NHS practice for those populations and could therefore be excluded. The committee concluded that the company had included the most relevant comparators.

Clinical effectiveness

Glecaprevir–pibrentasvir is effective for treating chronic hepatitis C

3.3 The key clinical evidence for glecaprevir–pibrentasvir came from 7 clinical trials. Only 1 trial included an active comparator (glecaprevir–pibrentasvir compared with sofosbuvir–daclatasvir). One trial was placebo controlled and the remaining 5 trials did not have a comparator. The trials included people who had not had treatment for their hepatitis C, and people whose hepatitis C had not adequately responded to interferon-based treatment or sofosbuvir plus ribavirin. Results showed that for all genotypes, irrespective of cirrhosis stage or treatment history, the rate of sustained virological response at 12 weeks after the end of treatment ranged from 87.5% to 100.0%. The ERG noted that patient numbers in the trials were low and only 4 out of the 24 subgroups included more than 100 patients, which causes considerable uncertainty in the rates of sustained virological response. The committee was aware that patient numbers would be low in some subgroups because of the low incidence of disease of certain genotypes. The clinical experts stated that glecaprevir–pibrentasvir is considered similar in effectiveness to the new direct-acting antiviral drugs. The committee concluded that glecaprevir–pibrentasvir is effective for treating chronic hepatitis C across all subgroups and in all genotypes.

Glecaprevir–pibrentasvir is generally well tolerated

3.4 The most commonly reported adverse events with glecaprevir–pibrentasvir are headache and fatigue. The committee noted the relatively favourable safety and tolerability profile, irrespective of cirrhosis stage, treatment experience and degree of renal impairment. The clinical experts stated that glecaprevir–pibrentasvir has a similar tolerability profile to other direct-acting antiviral regimens. The committee concluded that the adverse events associated with glecaprevir–pibrentasvir were generally tolerable.

Cost-effectiveness analysis

The company's model structure is acceptable for decision-making

3.5 The structure of the company's model and its assumptions about the natural history of the disease including distinguishing between no cirrhosis (further subdivided into fibrosis severity) and compensated cirrhosis was similar to models used for other NICE technology appraisals for chronic hepatitis C. The model did not include onward transmission of disease or reinfection. In its scenario analyses, the ERG explored using reinfection rates from Simmons et al. (2016), which calculated the reinfection probability as 0.0033. This had no impact on the results. The committee had previously accepted similar models that excluded disease transmission and reinfection, so it concluded that the structure of the model was acceptable for decision-making.

The company's naive indirect comparison leads to uncertainty in the model results

3.6 The company used a naive indirect comparison to compare glecaprevir–pibrentasvir with the relevant comparators. Due to the lack of comparative trial data for glecaprevir–pibrentasvir and the comparators a conventional indirect treatment comparison was not feasible. The rates of sustained virological response for the comparators in the company's model were selected from individual arms of randomised controlled trials. The company had used some of the same

rates of sustained virological response for comparator technologies as those used in the NICE technology appraisal guidance on sofosbuvir–velpatasvir. The rates of sustained virological response for the direct-acting antivirals were similar to those for glecaprevir–pibrentasvir in its trials. The ERG stated that the company's choice of study for each comparator was often arbitrary. The committee noted that this approach meant that the results were at risk of the kind of bias normally associated with observational studies. It concluded that the company's method of estimating efficacy in the model introduced some uncertainty in the results.

The company's transition probabilities are appropriate for decision-making

3.7 The company used the same sources for non-treatment-specific transition probabilities as those used in previous NICE technology appraisals on hepatitis C. These included Thein et al. (2008) and Kanwal et al. (2014) for fibrosis progression, and Cardoso et al. (2010) and Fattovich et al. (1997) for non-fibrosis progression. The committee was generally satisfied with this approach. In a scenario analysis, the ERG explored using Grishchenko et al. (2009) which had also been accepted for fibrosis progression in previous appraisals, but this had no impact on the results. The committee therefore concluded that the company's transition probabilities were appropriate for decision-making.

The company's utility values are acceptable for decision-making

3.8 In its base-case analyses, the company used utility data from the literature (Wright et al. 2006) in line with the previous NICE technology appraisals on hepatitis C to inform the difference in utility of a health state with or without sustained virological response. In a scenario analysis the company used utility data collected from clinical trials using the EQ-5D, but this did not change the results. The average sustained virological response-related utility increments from the company's trials (0.025 to 0.029) were smaller than that from Wright et al. (0.05), which has consistently been used in previous hepatitis C NICE technology appraisals. The ERG explored the impact of applying a zero gain in utility after sustained virological response but this also had no impact on the

results. None of the other utility scenario analyses done by the ERG had any significant impact on the results. The committee therefore accepted the company's base-case utility estimates but emphasised that in future hepatitis C appraisals, utility values from the literature will no longer be considered acceptable if there are appropriate utility values collected from clinical trials.

Cost-effectiveness results

Glecaprevir–pibrentasvir is cost effective and is therefore recommended

3.9 Using the confidential price discounts for glecaprevir–pibrentasvir and its comparators (where applicable), the results showed that glecaprevir–pibrentasvir was the most cost-effective treatment in all groups (with incremental cost-effectives ratios [ICERs] substantially below £20,000 per quality-adjusted life year [QALY] gained), except for people with untreated genotype 4 HCV without cirrhosis. In this group glecaprevir–pibrentasvir was the cheapest treatment with the lowest total QALYs. The company's deterministic sensitivity analysis showed that the model was primarily driven by the rates of sustained virological response, which the committee had previously concluded led to uncertainty in the model (section 3.6). The committee was aware that the rate of sustained virological response used to inform this subgroup analysis (untreated genotype 4 HCV without cirrhosis) was based on small patient numbers and was lower than those used for the comparators. The clinical experts had stated that glecaprevir–pibrentasvir is considered similar in effectiveness to the new direct-acting antiviral drugs (section 3.3), and considered that any difference in sustained virological response rate was probably a result of the small patient numbers in the group. The committee recalled the clinical experts' comments (section 3.1) that glecaprevir–pibrentasvir is likely to be effective in all subgroups regardless of genotype, treatment history or cirrhosis status. It also recalled that glecaprevir–pibrentasvir was the most cost-effective treatment in all of the other genotype 4 subgroups. In addition, because of the small patient numbers of people with genotype 4 HCV, it had previously accepted sustained virological

response rates from genotype 1 as a proxy for genotype 4 rates in some hepatitis C appraisals. Therefore on the balance of evidence available, the committee considered that glecaprevir–pibrentasvir would be equally cost effective for treating genotype 4, previously untreated chronic hepatitis C in people without cirrhosis. The committee concluded that glecaprevir–pibrentasvir could be recommended within its marketing authorisation as a cost-effective use of NHS resources for treating hepatitis C.

Other factors

Treatment and prescribing decisions

3.10 Previous NICE technology appraisal guidance on hepatitis C included recommendations on treatment and prescribing decisions because of capacity constraints within the NHS. The clinical experts stated that many people eligible for treatment, particularly people with cirrhosis, have now been treated, creating additional capacity to treat more. The clinical experts also stated that having more affordable drugs with shorter treatment durations also creates additional capacity. However, NHS England commented that there is considerable value in recommending that multidisciplinary teams in the operational delivery networks should prioritise treatment for people with the highest unmet clinical need. NHS England considers that the capacity constraints in the NHS have not changed sufficiently and that not including this recommendation would create major challenges. On balance, the committee accepted that it was appropriate to include the recommendation on treatment and prescribing decisions (see section 1.2) as in previous NICE guidance on hepatitis C treatments.

Innovation

3.11 The committee considered whether glecaprevir–pibrentasvir could be considered innovative, and whether the company's economic analysis had captured all associated health-related benefits. The committee agreed with the company that there is an unmet need for interferon-free regimens to treat people with previously treated genotype 3 hepatitis C,

particularly those with severe renal impairment. However, the committee concluded that it had taken these potential benefits into account when considering the cost effectiveness of glecaprevir–pibrentasvir.

Equality

3.12 The committee noted potential equality issues raised during the NICE scoping process that there are proportionately more people from Asian and minority ethnic groups, and more people who inject drugs, who have genotype 3 or genotype 4 HCV than other HCV genotypes. Having decided that glecaprevir–pibrentasvir should be recommended for all genotypes, the committee agreed that its recommendations for these groups would not have a different effect on people protected by equality legislation than on the wider population.

4 Implementation

4.1 Section 7(6) of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication. Because glecaprevir–pibrentasvir has been available through the Early Access to Medicines Scheme, NHS England and commissioning groups have committed to providing funding to implement this guidance 30 days after publication.

4.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal determination.

4.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has hepatitis C and the doctor responsible for their care thinks that glecaprevir–pibrentasvir is the right treatment, it should be available for use, in line with NICE's recommendations.

4.4 The contract prices used for decision-making in this appraisal are the relevant prices that the NHS pays for glecaprevir–pibrentasvir. These are based on contract pricing arrangements between the company and the Commercial Medicines Unit. The contract prices are commercial in confidence. Any enquiries from NHS organisations about the contract prices used in this appraisal should be directed to the Commercial Medicines Unit.

5 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee D.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

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NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

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Accreditation