[GUIDANCE IS OUTDATED AND HAS BEEN WITHDRAWN ON 3 JUNE 2024.]

Direct-acting antiviral agents

for treating genotype 2 to 6 chronic hepatitis C

Technology Guidance from the MOH Drug Advisory Committee

Guidance Recommendations

The Ministry of Health's Drug Advisory Committee has recommended:

- ✓ Sofosbuvir 400 mg/velpatasvir 100 mg tablet for treating genotype 2, 3, 4, 5, or 6 chronic hepatitis C infection in treatment-naïve, or pegylated interferon plus ribavirin (PR)-experienced or NS3/4A protease inhibitor (boceprevir, simeprevir, telaprevir)-experienced adults; and
- ✓ Glecaprevir 100 mg/pibrentasvir 40 mg tablet for treating genotype 2, 3, 4, 5, or 6 chronic hepatitis C infection in treatment-naïve, or pegylated interferon plus ribavirin (with or without sofosbuvir)-experienced, or sofosbuvir plus ribavirin-experienced adults.

Sofosbuvir/velpatasvir and glecaprevir/pibrentasvir should be used in line with the recommended treatment regimens listed in the Annex.

Sofosbuvir/velpatasvir and glecaprevir/pibrentasvir should be prescribed by a specialist physician (gastroenterologist, hepatologist, or infectious disease specialist) with experience in treating hepatitis C.

The supplier of sofosbuvir/velpatasvir will provide retreatment with sofosbuvir/velpatasvir/voxilaprevir to patients who fail to achieve a sustained virological response with sofosbuvir/velpatasvir through their *No Cure No Pay* program, at no additional cost.

Subsidy status

Sofosbuvir 400 mg/velpatasvir 100 mg tablet and glecaprevir 100 mg/pibrentasvir 40 mg tablet are recommended for inclusion on the Medication Assistance Fund (MAF), for the abovementioned indications.

A clinical checklist must be completed for all patients who are prescribed with either treatment through MAF. Clinical outcome data will also be collected by MOH for each patient after they have completed their treatment course.

MAF assistance **does not** apply to other direct-acting antivirals (sofosbuvir, sofosbuvir/velpatasvir/voxilaprevir, sofosbuvir+daclatasvir, sofosbuvir/ledipasvir and elbasvir/grazoprevir).

Update published on 4 January 2021

Factors considered to inform the recommendations for subsidy

Technology evaluation

1.1 The MOH Drug Advisory Committee ("the Committee") considered the evidence presented for the technology evaluation of direct-acting antivirals (DAAs; elbasvir/grazoprevir, sofosbuvir, sofosbuvir+daclatasvir, sofosbuvir/ledipasvir, sofosbuvir/velpatasvir, and sofosbuvir/velpatasvir/voxilaprevir) for treating genotype (GT) 2 to 6 chronic hepatitis C in August 2018. The Agency for Care Effectiveness conducted the evaluation in consultation with clinical experts from the public healthcare institutions. Published clinical evidence for the DAAs was considered in line with the registered indications for each product. The use of any DAA for retreatment after DAA failure was outside the scope of the evaluation.

1.2 The evidence was used to inform the Committee's deliberations around four core decision-making criteria:

- Clinical need of patients and nature of the condition;
- Clinical effectiveness and safety of the technology;
- Cost-effectiveness (value for money)—the incremental benefit and cost of the technology compared to existing alternatives; and
- Estimated annual technology cost and the number of patients likely to benefit from the technology.

1.3 Additional factors, including social and value judgments, may also inform the Committee's subsidy considerations.

1.4 In March 2020, the Committee considered subsidy listing of glecaprevir/pibrentasvir following regulatory approval by the Health Sciences Authority (HSA) in December 2018.

Clinical need

2.1 International clinical practice guidelines recommend DAAs to cure hepatitis C virus (HCV) infections, prevent progression to liver failure and liver cancer, and reduce mortality risk.

2.2 In August 2018, the Committee acknowledged that the World Health Organization (WHO) had recommended DAAs as essential medicines, and local clinicians aimed to align clinical practice with international treatment guidelines. However, because of high DAA treatment costs, patients often delayed treatment ('watch and wait')

until they had significant fibrosis, or were treated with a combination of pegylated interferon (once weekly as a subcutaneous injection) plus twice-daily oral ribavirin (PR regimen) in local practice. The Committee understood PR to be associated with high treatment burden because of its long treatment duration (24 to 48 weeks), rigorous dosing requirements, and significant side effects. PR is also contraindicated in some patients, such as those with decompensated cirrhosis (Child-Pugh B or C).

2.3 The Committee noted that HCV is divided into six distinct genotypes and genotypes 2 to 6 account for approximately 50% of cases in the general population (excluding prison inmates). The Committee noted that the true prevalence of hepatitis C was difficult to establish because many patients are asymptomatic and unaware of infection until severe symptoms present. However, based on expert opinion, at a diagnosis rate of 3% in 2018, there were approximately 1,443 people with genotype 3 and 624 people with either genotype 2, 4, 5 or 6 chronic hepatitis C in the general population requiring treatment over the next five years.

2.4 The Committee acknowledged that sofosbuvir/velpatasvir had already been recommended for listing on the MAF for genotype 1 chronic hepatitis C at a previous meeting in April 2018, and agreed that there was a high clinical need to subsidise DAAs for the remaining genotypes (2 to 6), to align local patient care with international best practice, and reduce the prevalent viral load in the general population.

Clinical effectiveness and safety

3.1 The Committee agreed that for DAAs, PR was the appropriate comparator. The DAA regimens were also compared with one other.

3.2 The Committee noted that most of the included DAA clinical studies were single-arm and did not compare directly with PR. Based on pooled estimates from meta-analyses conducted by ACE, the DAAs were associated with:

- Higher sustained virological response rates (see table) at 12 weeks (SVR12; cure) than those historically reported for PR (51% [95% CI 49% to 52%]);

Sustained virological response (SVR12) rates for DAAs *(Source: ACE meta-analyses of single-arm DAA trials)*
▪ GT2: 97.7% (95% CI 96.0% to 99.1%) ▪ GT3: 93.6% (95% CI 91.4% to 95.6%) ▪ GT4: 95.1% (95% CI 90.5% to 98.4%) ▪ GT5: 97.3% (95% CI 93.0% to 99.8%) ▪ GT6: 99.2% (95% CI 96.7% to 100%)

- Lower rates of serious adverse events (2.7% [95% CI 2.0% to 3.6%]) than PR (7.1% [95% CI 6.8% to 7.4%]); and

- Lower rates of treatment discontinuation because of adverse events (0.3% [95% CI 0.1% to 0.8%]) than PR (12% [95% CI 11% to 14%]).

3.3 The Committee noted that no head-to-head trials directly compared the DAAs with one other, and indirect comparisons were limited by the lack of a comparator arm in the single-arm studies to form connected trial networks. According to local clinicians, DAA regimens that demonstrated SVR12 rates ≥90% could be considered clinically comparable. The Committee noted that the pan-genotypic DAAs (which cover all genotypes 1 to 6; sofosbuvir/velpatasvir/voxilaprevir, and sofosbuvir/velpatasvir) consistently achieved SVR12 rates ≥90% for genotypes 2 to 6. Furthermore, sofosbuvir/ledipasvir (genotypes 4 to 6), elbasvir/grazoprevir (genotype 4) and sofosbuvir+daclatasvir (genotype 3) also achieved SVR12 rates ≥90% for their respectively indicated genotypes. Results for sofosbuvir+ribavirin did not consistently achieve target SVR rates. Based on available evidence, the Committee agreed that all the DAAs regimens, except sofosbuvir+ribavirin, could be regarded as a class for their indicated genotypes, as all had SVR rates ≥90%, with overlapping confidence intervals in the meta-analyses. There was no evidence available to demonstrate superior comparative effectiveness or safety of one DAA regimen over another.

3.4 In March 2020, the Committee noted that glecaprevir/pibrentasvir (a pan-genotypic DAA) also consistently achieved SVR12 rates ≥90% for genotypes 2 to 6, and concluded that it was clinically comparable to the other DAAs.

Cost effectiveness

4.1 ***Cost-minimisation among the DAAs***

In August 2018, the Committee agreed that a cost-minimisation approach was appropriate in selecting the lowest-priced DAA for subsidy consideration in view of comparable clinical effectiveness and safety across all drugs within the class. It noted that the manufacturer for sofosbuvir, sofosbuvir/ledipasvir, and sofosbuvir/velpatasvir/voxilaprevir did not submit a value-based pricing (VBP) proposal for subsidy consideration of these drugs. Among the DAAs with VBP proposals, the manufacturer of sofosbuvir/velpatasvir offered the lowest price. As a result, the Committee did not recommend the other DAAs (sofosbuvir, sofosbuvir+daclatasvir, sofosbuvir/ledipasvir, sofosbuvir/velpatasvir/voxilaprevir and elbasvir/grazoprevir) for subsidy.

4.2 The Committee acknowledged that the supplier of sofosbuvir/velpatasvir committed to provide retreatment with sofosbuvir/velpatasvir/voxilaprevir through their 'No Cure No Pay' program at no additional cost for patients who fail to achieve a sustained virological response with sofosbuvir/velpatasvir as part of their VBP proposal.

4.3

In March 2020, following a price proposal from the manufacturer, the Committee agreed that the cost of glecaprevir/pibrentasvir was reasonable compared to other DAAs and could be considered an acceptable use of healthcare resources.

Estimated annual technology cost

5.1 In August 2018, the Committee noted the annual cost impact was estimated at SG$1 million to SG$3 million in the first year of listing sofosbuvir/velpatasvir on the MAF. In March 2020, the Committee agreed that no additional subvention amount was required to include glecaprevir/pibrentasvir on the MAF as patients would only receive one DAA.

Additional considerations

6.1 The Committee acknowledged that more patients may seek treatment if DAAs are listed on the MAF, and advised prescribing clinicians to explore a risk-based approach for prioritising patients needing treatment to manage capacity issues.

6.2 The Committee noted that improved treatment access and lower viral loads circulating in the local community could also lead to broader population benefits.

Recommendation

7.1 Based on available evidence presented in August 2018, the Committee recommended sofosbuvir 400 mg/velpatasvir 100 mg tablet be listed on the MAF for treating genotype 2 to 6 chronic hepatitis C given its favourable clinical and cost effectiveness, and the high clinical need for DAA treatment for these genotypes to ensure appropriate patient care.

7.2 In March 2020, the Committee also recommended glecaprevir 100 mg/pibrentasvir 40 mg tablet be listed on the MAF, following an acceptable price proposal from the manufacturer.

ANNEX

Treatment duration recommendations by genotype, treatment status and cirrhosis status

Patient population	Direct-acting antivirals	
	Sofosbuvir/ velpatasvir	Glecaprevir/ pibrentasvir
Treatment-naïve patients with HCV (genotype 2 to 6) without cirrhosis	12 weeks	8 weeks
Treatment-naïve patients with HCV (genotype 2 to 6) with compensated cirrhosis (Child-Pugh A)	12 weeks	8 weeks
Treatment-naïve patients with HCV (genotype 2 to 6) with decompensated cirrhosis (Child-Pugh B or C)	12 weeks in combination with ribavirin	-
Treatment-experienced (failed prior therapy with peg-IFN+ribavirin or NS3/4A protease inhibitor [boceprevir, simeprevir, telaprevir]) patients with HCV (genotype 2 to 6) without cirrhosis	12 weeks	-
Treatment-experienced (failed prior therapy with peg-IFN+ribavirin or NS3/4A protease inhibitor [boceprevir, simeprevir, telaprevir]) patients with HCV (genotype 2 to 6) with compensated cirrhosis (Child-Pugh A)	12 weeks	-
Treatment-experienced (failed prior therapy with peg-IFN+ribavirin or NS3/4A protease inhibitor [boceprevir, simeprevir, telaprevir]) patients with HCV (genotype 2 to 6) with decompensated cirrhosis (Child-Pugh B or C)	12 weeks in combination with ribavirin	-
Treatment-experienced (failed prior therapy with peg-IFN+ribavirin±sofosbuvir, or sofosbuvir+ribavirin) patients with HCV (genotype 2,4,5,6) without cirrhosis	-	8 weeks
Treatment-experienced (failed prior therapy with peg-IFN+ribavirin±sofosbuvir, or sofosbuvir+ribavirin) patients with HCV (genotype 2,4,5,6) with compensated cirrhosis (Child-Pugh A)	-	12 weeks
Treatment-experienced (failed prior therapy with peg-IFN+ribavirin±sofosbuvir, or sofosbuvir+ribavirin) patients with HCV (genotype 3) without cirrhosis	-	16 weeks
Treatment-experienced (failed prior therapy with peg-IFN+ribavirin±sofosbuvir, or sofosbuvir+ribavirin) patients with HCV (genotype 3) with compensated cirrhosis (Child-Pugh A)	-	16 weeks
Key: HCV, hepatitis C virus; peg-IFN, pegylated interferon		

VERSION HISTORY

Guidance on direct-acting antiviral agents
for treating genotype 2 to 6 chronic hepatitis C

This Version History is provided to track any updates or changes to the guidance following the first publication date. It is not part of the guidance.

Publication of guidance
Date of Publication 2 Jan 2019

Guidance updated to acknowledge implementation of the 'No Cure No Pay' retreatment program for patients who fail to achieve a sustained virological response with sofosbuvir/velpatasvir
Date of Publication 2 Sep 2019

Guidance updated to include MAF listing of glecaprevir/pibrentasvir
Date of Publication 4 Jan 2021

About the Agency

The Agency for Care Effectiveness (ACE) is the national health technology assessment agency in Singapore residing within the Ministry of Health. It conducts evaluations to inform the subsidy of treatments, and produces guidance on the appropriate use of treatments for public hospitals and institutions in Singapore. The guidance is based on the evidence available to the Committee as at 31 August 2018 and 20 March 2020. This guidance is not, and should not be regarded as, a substitute for professional or medical advice. Please seek the advice of a qualified healthcare professional about any medical condition. The responsibility for making decisions appropriate to the circumstances of the individual patient remains with the healthcare professional.

Find out more about ACE at www.ace-hta.gov.sg/about

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