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Drugs for Chronic Hepatitis C Infection — Project Protocol

Supporting Informed Decisions

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This report was prepared by CADTH in collaboration with the Canadian Institutes of Health Research (CIHR) Drug Safety and Effectiveness Network (DSEN). This report contains a comprehensive review of existing public literature, studies, materials, and other information and documentation (collectively the "source documentation") available to CADTH at the time it was prepared, and it was guided by expert input and advice throughout its preparation.

The information in this report is intended to help health care decision-makers, patients, health care professionals, health systems leaders, and policy-makers make well-informed decisions and thereby improve the quality of health care services. The information in this report should not be used as a substitute for the application of clinical judgment in respect to the care of a particular patient or other professional judgment in any decision-making process, nor is it intended to replace professional medical advice. While CADTH has taken care in the preparation of this report to ensure that its contents are accurate, complete, and up-to-date, CADTH does not make any guarantee to that effect. CADTH is not responsible for any errors or omissions or injury, loss, or damage arising from or as a result of the use (or misuse) of any information contained in or implied by the information in this report. CADTH takes sole responsibility for the final form and content of this report. The statements, conclusions, and views expressed herein do not necessarily represent the view of Health Canada or any provincial or territorial government.

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ABBREVIATIONS

CDEC	Canadian Drug Expert Committee
CHC	chronic hepatitis C
DAA	direct-acting antiviral agent
FDC	fixed-dose combination
HBV	hepatitis B
HCV	hepatitis C virus
HIV	human immunodeficiency virus
PR	pegylated interferon alfa combined with ribavirin
RGT	response-guided therapy
RCT	randomized controlled trial
SDT	standard (or fixed) duration therapy
SVR	sustained virological response
TB	tuberculosis

1. BACKGROUND

Approximately 242,000 Canadians are infected with chronic hepatitis C virus (HCV) and the number grows by an estimated 7,900 new infections each year.[1] Prevalence and incidence may be underestimated, as many patients are unaware that they are infected. HCV-infected persons progress through various stages of disease and in due course may develop critical illnesses resulting from associated sequelae.[2,3] It is estimated that 15% to 25% of patients with chronic HCV infection will develop hepatocellular carcinoma or progressive liver disease within 20 years of infection, resulting in liver transplantation for some, and decreased life expectancy and quality of life for many.[4,5] The lifetime risk of developing complications of HCV may be higher than 25% because many individuals are infected for much longer than 20 years.

HCV can be divided into six unique genotypes, each with one or more subtypes. Genotype 1 is the most common in Canada (55% to 65%) and historically the most difficult to cure.[6,7] Genotypes 2 and 3 are the next most common, estimated to comprise 14% and 20% of HCV infections in Canada, respectively. Genotypes 4, 5, and 6 are less common in Canada and account for less than 5% of HCV cases.[6,8] Until 2011, standard of care for HCV was based on the use of pegylated interferon alfa combined with ribavirin (PR).[9] Following regulatory approvals beginning in 2011, combinations of the direct-acting antiviral agents (DAAs) boceprevir, telaprevir, simeprevir, and sofosbuvir with PR demonstrated greater efficacy in terms of sustained virological response (SVR) than PR alone in clinical studies, resulting in a changed paradigm for management of patients with chronic HCV genotype 1 infection.[10,11] In 2014, CADTH completed a Therapeutic Review of treatments for chronic HCV genotype 1 infection that included the available DAA-based regimens.[12] Based on this review, the Canadian Drug Expert Committee (CDEC) recommended that:[13]

- DAA plus PR treatment should be offered only to persons with chronic HCV infection who have fibrosis stages F2, F3, or F4.
- Simeprevir daily for 12 weeks, in combination with PR for 24 to 48 weeks, should be used as the protease inhibitor of choice for treatment-naive patients or for treatment-experienced patients with prior relapse.
- Persons in whom a DAA plus PR regimen has failed should not be re-treated with another DAA plus PR regimen.

At that time, CDEC could make no definitive recommendations regarding the place in therapy for sofosbuvir relative to other available protease inhibitors.

Despite the improved efficacy of these new treatment regimens, they may be associated with significant side effects, long treatment schedules, and limited success in specific HCV genotypes.[14] A number of interferon-free treatment regimens have recently entered the market or are in late-stage development. Early evidence suggests improved tolerability and higher rates of SVR in both treatment-naive and treatment-experienced patients with or without cirrhosis, as well as shorter treatment durations, compared with interferon-based regimens.[15]

The FDA and Health Canada have approved Harvoni (an interferon-free combination of ledipasvir and sofosbuvir) and recently gave approval to Holkira Pak (known in the United States as Viekira Pak), a combination of a dasabuvir tablet and an ombitasvir, paritaprevir, and ritonavir tablet, which may also be combined with ribavirin.[16,17] Interferon-free regimens containing daclatasvir and asunaprevir have been submitted to the CADTH Common Drug Review (CDR) as pre-NOC (Notice Of Compliance) submissions, suggesting that they may be approved by Health Canada in the near future.[18,19] A number of other treatment regimens are in phase 3 clinical trial programs that span multiple genotypes and address more specific

subgroups of HCV patients, including those with HIV co-infection, decompensated liver disease, and liver transplant.[20] Regulatory approvals have given way to discussions of affordability and accessibility, which pose a challenge for both publicly and privately funded drug programs in Canada, given the high cost of treatments for chronic HCV infection. Additional challenges for decision- and policy-makers in assessing newer regimens for chronic HCV infection include methodological limitations in the evidence base, such as the lack of control groups, that make it difficult to compare treatments using conventional means.[21]

In anticipation of the need and demand for supporting evidence and information regarding the comparative effectiveness of new regimens for chronic HCV infection, CADTH is updating its Therapeutic Review to include recently approved and emerging regimens for the treatment of chronic HCV infection (genotypes 1 through 6), including interferon-free regimens.

2. PROTOCOL DEVELOPMENT

To inform the final scope of the therapeutic review and protocol development, a proposed scope was posted to the CADTH website for stakeholder feedback. In addition, patient-group input was solicited. Throughout the planning and consultation process, patients, clinicians, and other stakeholders have clearly expressed the need for more effective, safer, and less burdensome therapies for chronic hepatitis C (CHC) infection. Recent studies involving new treatments for CHC infection, including pan-genotypic DAAs, all-oral fixed-dose combinations, and interferon-free treatment regimens, are now available. Although many of these treatments have not been approved for use by Health Canada, stakeholders have expressed interest in a synthesis of evidence on existing and emerging therapies across all genotypes (1 through 6) for patients with CHC infection, given the rapidly changing landscape of this therapeutic area. Therefore, the therapeutic review protocol includes treatments currently approved by Health Canada for patients with CHC infection; interferon-free regimens that are likely to be approved in Canada in the coming months based on pre-NOC submissions to CDR and on information gathered from publicly available sources, and through dialogue with clinical experts; and regimens recommended in Canadian and US guidelines.[22] The regimens identified as being in scope for this review reflect the information available to CADTH as of February 2015.

3. DELIVERABLES

The following deliverables are planned:

- A science report, including both an updated systematic review of the efficacy and safety of in-scope regimens for the treatment of CHC infection, as well as an assessment of cost-effectiveness based on a cost-utility economic analysis.
- CDEC Recommendations and/or Advice based on the science report and stakeholder feedback. CADTH will not develop recommendations on treatment regimens that have not been approved by Health Canada at the time of CDEC deliberations.

4. POLICY QUESTIONS

There are three proposed policy questions for this project. These reflect the information needs of CADTH's jurisdictional clients.

1. How should interferon-free DAA regimens be listed for reimbursement for CHC infection (genotypes 1 to 6)?
2. Should reimbursement of regimens for CHC infection be guided by fibrosis staging and limited to fibrosis stages ≥ F2?
3. Should re-treatment with a DAA regimen be reimbursed for patients with CHC infection who fail to achieve SVR on another DAA regimen?

5. RESEARCH QUESTIONS

Five research questions were developed to address the aforementioned policy issues.

1. What is the comparative efficacy and safety of treatment regimens for patients with CHC infection (genotypes 1 to 6) who are *treatment naive*?
2. What is the comparative cost-effectiveness of treatment regimens for patients with CHC infection (genotypes 1 to 4) who are *treatment naive*?*
3. What is the comparative efficacy and safety of treatment regimens for patients with CHC infection (genotypes 1 to 6) who have *relapsed or had a partial or null response* to prior PR or DAA + PR or DAA-only therapy?
4. What is the comparative cost-effectiveness of treatment regimens for patients with CHC infection (genotypes 1 to 4) who have *relapsed or had a partial or null response* to prior PR or DAA + PR or DAA-only therapy?*
5. *For questions 1 to 4*, how do the comparative efficacy, safety, and cost-effectiveness of treatment regimens vary across population subgroups based on fibrosis level (Metavir Score ≤ F1, F2, F3, or F4), cirrhosis stage (e.g., compensated versus decompensated), genotype subtype, post-liver transplant, baseline viral load, HIV/HCV co-infection, hepatitis B (HBV)/HCV co-infection, and tuberculosis (TB)/HCV co-infection?

* The decision to model cost-effectiveness only for HCV genotypes 1 to 4 was based on the anticipated availability of sufficient clinical data to inform the analysis.

6. METHODS

6.1 Literature Search Strategy

The literature search will be performed by an information specialist using a peer-reviewed search strategy. This search will update the original search run for the 2014 CADTH Therapeutic Review on DAAs for chronic hepatitis C genotype 1. Reviewers will re-screen the original search results for studies examining genotypes 2 through 6. The updated search will incorporate several additional DAAs, while excluding the results of the original search. The updated search results will be screened for all genotypes (1 through 6).

Published literature will be identified by searching the following bibliographic databases: MEDLINE (1946–) with in-process records & daily updates via Ovid; Embase (1974–) via Ovid;

Cochrane Central Register of Controlled Trials via Ovid; and PubMed. The search strategy will consist of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts are telaprevir, boceprevir, sofosbuvir, simeprevir, ledipasvir, paritaprevir, ombitasvir, dasabuvir, daclatasvir, asunaprevir, grazoprevir, elbasvir, beclabuvir, GS-5816, ABT-530, Incivek, Incivo, Victrelis, Sovaldi, Galexos, Olysio, Daklinza, Sunvepra, Viekira, Viekirax, Exviera, Holkira, and Harvoni.

No filters will be applied to limit the retrieval by study type. Where possible, retrieval will be limited to the human population. Retrieval will not be limited by publication date but will be limited to English language results. Conference abstracts will be excluded from the search results. Regular alerts will be established to update the search until recommendations by CDEC. Regular search updates will be performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) will be identified by searching relevant websites from the following sections of the Grey Matters: A Practical Search Tool for Evidence-Based Medicine checklist (http://www.cadth.ca/resources/grey-matters): health technology assessment agencies, health economics, clinical practice guidelines, drug and device regulatory approvals, advisories and warnings, drug class reviews and databases (free). Google and other Internet search engines will be used to search for additional web-based materials. These searches will be supplemented by reviewing the bibliographies of key papers and through contacting appropriate experts.

6.2 Selection Criteria

6.2.1 Clinical

Two reviewers will independently screen titles and abstracts for relevance to the clinical research questions. Full texts of potentially relevant articles will be retrieved and independently assessed for possible inclusion based on the predetermined selection criteria (Table 1). The two reviewers will then compare their chosen included and excluded studies; disagreements will be discussed until consensus is reached. The study selection process will be presented in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart.[23]

Table 1: Inclusion and Exclusion Criteria for Primary Studies	
Inclusion Criteria	
Population	Adults with CHC infection (genotypes 1 through 6)
Interventions/ Comparators	Currently available: • PR[a] • boceprevir + PR[a] • telaprevir + PR[a] • simeprevir + PR • sofosbuvir + PR • sofosbuvir/ledipasvir (with or without RBV) • paritaprevir/ritonavir/ombitasvir + dasabuvir (with or without RBV) • sofosbuvir + ribavirin • simeprevir + sofosbuvir (with or without RBV) • daclatasvir + asunaprevir (with or without PR) • daclatasvir + sofosbuvir Emerging: • daclatasvir + asunaprevir + beclabuvir (with or without RBV) • grazoprevir + elbasvir (with or without RBV) • sofosbuvir + GS-5816 (with or without RBV) • paritaprevir/ritonavir + ABT-530 (with or without RBV) (See Appendix 1for a detailed list of regimens eligible for inclusion in the review.)
Outcomes	• SVR rate at 12 weeks and 24 weeks • Relapse • Quality of life • Hepatic cirrhosis • Hepatocellular carcinoma • Liver transplants • Mortality (all-cause, liver-related) • Serious adverse events • Withdrawals due to adverse events • Rash • Fatigue • Anemia • Thrombocytopenia • Pruritus • Neutropenia • Depression • Suicidal ideation • Flu-like symptoms
Study Design	Published, randomized or non-randomized, controlled or uncontrolled, prospective interventional studies
Exclusion Criteria	
Studies will be excluded if they are in languages other than English; are presented in abstract format; do not meet the aforementioned selection criteria; provide results of a qualitative study; are follow-up, extension, or observational studies. Duplicate publications, narrative reviews, conference abstracts, and editorials will also be excluded.	

CHC = chronic hepatitis C; DAA = direct-acting antiviral; PR = pegylated interferon alfa + ribavirin; RCT = randomized controlled trial; RBV = ribavirin; SVR = sustained virologic response; vs. = versus.
[a] Included in the analysis primarily as a comparator for other regimens.

Regimens eligible for inclusion in the review are those that have been approved by Health Canada, are considered of clinical relevance based on expert advice or Canadian or US clinical practice guidelines, or have a high likelihood of regulatory approval in Canada in the near future (i.e., within approximately 12 months) based upon information available to CADTH as of February 2015. Some regimens containing PR require a lead-in period or are eligible for changes in the duration of PR therapy based on viral response (i.e., response-guided therapy [RGT]); the rules for inclusion of such regimens will be the same as in the original CADTH Therapeutic Review.[12] For patients with HIV co-infection or those who are treated following liver transplantation, dosing regimens other than those described in Appendix 1 may be eligible for inclusion, given that potential drug interactions between antiretroviral and immunosuppressant agents may require dosage adjustments of HCV medications.

It is acknowledged that the older regimens for CHC infection (PR alone, boceprevir, telaprevir) are of limited clinical significance, given the availability of newer regimens; telaprevir has in fact been discontinued from the Canadian market by the manufacturer. However, Health Canada–approved regimens containing these agents will be retained in the review and meta-analysis for comparative purposes. Only randomized controlled trials (RCTs) of such regimens will be eligible for inclusion. For all other regimens listed in Table 1, both RCTs and non-randomized interventional studies (including single-arm trials) will be eligible for inclusion in the review. Observational studies such as cohort studies or reports describing experience from compassionate use programs will be excluded.

6.2.2 Economic

One reviewer will screen titles and abstracts relevant to the economic research questions on the use of available drug therapies for the treatment of patients with CHC infection that might inform data inputs in the health economic model. Full papers will be obtained for those that appear to be potentially relevant.

A search will also be performed to determine the availability of data to inform the natural history of genotypes 2 through 4 for the economic model, and the distribution of fibrosis scores for these genotypes.

6.3 Data Extraction and Critical Appraisal of Clinical Studies

One reviewer will perform data extraction for each article, using a data extraction form developed a priori and covering the following items:

- Study characteristics, key inclusion and exclusion criteria, and definitions where required
- Baseline patient characteristics, demographics, and treatment history
- Interventions evaluated, including dose and duration. Efficacy and safety results for specified outcomes, and specifically:
  - SVR at 12 and 24 weeks
  - Safety outcomes for the longest reported treatment and follow-up period.
- Type of analysis (intention-to-treat or per-protocol)
- Withdrawals
- Study-level definitions of SVR, prior relapse, partial or null response (if standard definitions were not employed), and cirrhosis.

For interventional, single-arm studies (i.e., where there is no formal comparative control group included in the design), detailed data will be extracted. The use of historical control cohorts and the results based on those cohorts will be captured, along with patient characteristics of the historical cohort where provided.

All extracted data will be checked for accuracy by a second reviewer. Any disagreements will be resolved through discussion until consensus is reached.

Quality assessment of comparative randomized studies will be performed independently by two reviewers using the Cochrane Risk of Bias tool.[24] We will endeavour to appraise the single-arm studies using criteria applicable for the evaluation of case series studies: http://www.ihe.ca/download/development_of_a_quality_appraisal_tool_for_case_series_studies_using_a_modified_delphi_technique.pdf. In the event that there are insufficient data for appraisal, we will thoroughly extract and investigate attrition rates.

6.4 Data Analysis and Synthesis

6.4.1 Clinical

Included studies will be classified based on study populations and relevant comparisons. Prior to quantitative pooling of study-specific outcomes, a thorough qualitative analysis will be undertaken to assess clinical and methodological heterogeneity. If substantial heterogeneity exists in certain comparisons or subsets of studies, then narrative summaries of findings will be reported.[25,26] In addition, clinical experts will be asked to identify relevant effect modifiers that may result in differences in treatment effect for SVR across all genotypes. In the previous Therapeutic Review, presence of cirrhosis (Metavir score = 4) in genotype 1 was identified as an important effect modifier. This variable will be confirmed with experts for the purposes of this review. Where appropriate, meta-analysis of direct comparisons and network meta-analyses (NMAs) for the purpose of indirect treatment comparisons may be performed.

The primary efficacy outcome will be SVR at 12 weeks. Separate analyses will be performed for each genotype, and within each genotype, analyses will be separated into subpopulations based on prior treatment experience with PR (with or without DAA), as follows:

- Treatment-naive
- Treatment-experienced
  - All
  - Relapsed
  - Prior partial response
  - Prior null response.

For studies that enrolled mixed populations (i.e., treatment-naive and -experienced patients), the analysis will target specific subpopulations rather than the entire study population, where data allow. In addition, studies in liver transplant patients will be analyzed separately due to the unique characteristics of this population with respect to disease prognosis.

Subgroup analyses will also be conducted where appropriate; these will include genotype subtypes (e.g., G1a versus G1b); baseline viral load (using study-defined thresholds); fibrosis stage (Metavir score F0 through F4); presence or absence of cirrhosis (if defined differently from Metavir score F4), and in patients with cirrhosis — compensated cirrhosis, advanced compensated cirrhosis, and decompensated cirrhosis; and HIV, TB, or HBV co-infection.

Bayesian NMAs will be conducted for the outcomes specified in Table 1 for both treatment-naive and treatment-experienced patients and for the key subgroups of interest. The choice of outcomes for NMA will be based on the sufficiency of the data available to derive robust and consistent network models. WinBUGS software version 1.4.3 (MRC Biostatistics Unit, Cambridge, UK) will be used to conduct NMA, considering models such as binomial likelihood model (dichotomous) or a normal likelihood model (continuous), which allows for the use of

multi-arm trials.[27,28] Both fixed and random effects NMAs will be considered, including both vague and informative priors on the between-study variance for random effects meta-analyses.[26] Choice of model will be based on assessment of model fit using the deviance information criterion and by comparing residual deviance to number of unconstrained data points.[29] Trace plots and the Brooks–Gelman–Rubin statistic will be used to assess convergence. Three chains will be fit in WinBUGS for each analysis, with at least 40,000 iterations and a burn-in of at least 10,000 iterations.

We anticipate that we will find single-arm interventional study designs. Such study designs will be eligible for inclusion in the review as described in Section 6.2.1. Single-arm interventional studies will need to be addressed in the meta-analyses and NMAs. Methods for incorporating these single-arm studies in the analysis include:

- Propensity score methods to best match the baseline characteristics of the single-arm study to a comparator group; however, this would require individual patient data, which would likely not be available.
- Construction of a comprehensive data listing of the baseline characteristics of comparator arms from the randomized studies and development of a virtual comparator arm using these data that best matches the single-arm study.
- Extension of the Bayesian hierarchical model with the formal insertion of a hypothetical single-arm trial into the model.

A hierarchical approach will be taken for data synthesis, with the base-case analyses (meta-analysis and/or NMA) limited to Health Canada–approved regimens, pre-NOC regimens submitted to CDR, and off-label regimens consisting of drugs for which cost information is available at the time of the economic analysis. Other regimens for which there are the appropriate clinical data, but cost information is lacking for one or more constituent drugs, will be included in secondary analyses of all in-scope regimens.

Any studies or data identified from stakeholder feedback to the Included Studies list (posted on the CADTH website) will be assessed for inclusion in the analyses and economic model. Any data identified subsequently (through search alerts or other means) may not be incorporated into the analyses or economic model but will be summarized narratively.

For genotype 1 studies, the evidence network from the previous Therapeutic Review[12] will be extended to include evidence included in the current review. Methods described above will be employed to link interferon-free regimens to the existing evidence base.

6.4.2 Economic

The economic evaluation will be based on a Markov model previously developed for adults with CHC genotype 1 infection.[12] Model inputs will be updated as necessary, and information regarding the natural history for patients with CHC genotypes 2 to 4 will be reviewed to determine what modifications might be needed. The primary analysis will be in the form of a cost-utility analysis comparing treatment regimens included in the base-case NMA in terms of the incremental cost per quality-adjusted life-year (incremental cost-utility ratio). The parameter uncertainty will be assessed through both deterministic and probabilistic sensitivity analyses.

6.5 Opportunities for Stakeholder Feedback

CADTH will formally solicit feedback from stakeholders at the following stages of the process for this therapeutic review:

- Identification of additional studies meeting inclusion criteria
- Feedback on draft Therapeutic Review report
- Feedback on draft CDEC therapeutic review recommendation(s).

A notice to the Calls for Feedback page will be posted and an email to subscribers of the CADTH E-Alert service will be sent. Instructions on providing feedback are included with every notification.

6.6 Data Availability

In accordance with the CADTH Therapeutic Review Framework: *"The primary source of data is in the public domain. All stakeholders will be given the option of identifying and providing unpublished data on the condition that, if used, it would be included in publicly available reports and documents, related to the therapeutic review."*[30] If the necessary clinical data required to address the research questions are not made publicly available prior to the data analysis stage of the Therapeutic Review, there may be limited information available to address all of the research or policy questions listed in this protocol.

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APPENDIX 1: REGIMENS ELIGIBLE FOR INCLUSION

GENOTYPE	INTERVENTION	DOSE	DURATION
Genotype 1	Pegylated interferon alfa-2a + RBV (PR)	Pegylated interferon alfa-2a 180 mcg once weekly + weight-based RBV if < 75 kg = 1,000 mg if ≥ 75 kg = 1,200 mg each day in two divided doses	48 weeks
	Pegylated interferon alfa-2b + RBV (PR)	Pegylated interferon alfa-2b 1.5 mcg per kg once weekly + weight-based RBV (800 mg to 1,400 mg) each day in two divided doses	48 weeks
	BOC + PR	BOC 800 mg t.i.d. + PR	Treatment-naive: PR weeks 1 to 4, then (a) BOC + PR weeks 5 to 28, if HCV RNA undetected at weeks 8, 12, and 24; or (b) BOC + PR weeks 5 to 28, then PR weeks 29 to 48 if HCV RNA detectable at week 8, < 100 IU/mL week 12, and undetectable at week 24. Prior relapse or Prior partial response: PR weeks 1 to 4, then (a) BOC + PR weeks 5 to 36, if HCV RNA undetectable at week 8, 12, and 24; or (b) BOC + PR weeks 5 to 36, then PR weeks 37 to 48, if HCV RNA detectable at week 8, < 100 IU/mL week 12, and undetectable at week 24. Prior null response, or patients with cirrhosis, or treatment-naive patients without cirrhosis but with a poor interferon response (< 1 log10 decline in HCV RNA at week 4): PR weeks 1 to 4, then BOC + PR weeks 5 to 48. Stopping rules: Stop all drugs if HCV RNA ≥ 100 IU/mL at week 12 or confirmed detectable at week 24.

GENOTYPE	INTERVENTION	DOSE	DURATION
	TEL + PR	TEL 750 mg t.i.d. or TEL 1,125 mg b.i.d. + PR	Treatment-naive, or Prior relapse: TEL + PR weeks 1 to 12, then (a) PR weeks 13 to 24, if HCV RNA undetected at weeks 4 and 12; or (b) PR weeks 13 to 48, if HCV RNA detectable (≤ 1,000 IU/mL) at weeks 4 or 12. Prior partial response, or Prior null response, or patients with Cirrhosis: TEL + PR weeks 1 to 12, then PR weeks 13 to 48. Stopping rules: Stop all drugs if HCV RNA ≥ 1,000 IU/mL at week 4 or 12, or confirmed detectable at week 24.
	SIM + PR	SIM 150 mg q.d. + PR	Treatment-naive (with or without cirrhosis), or Prior relapse (with or without cirrhosis): SIM + PR weeks 1 to 12, then (a) PR weeks 13 to 24, if HCV RNA undetectable at week 4; or (b) PR weeks 13 to 48, if HCV RNA < 25 IU/mL detectable at week 4. Prior partial response (with or without cirrhosis), or Prior null response (with or without cirrhosis): SIM + PR weeks 1 to 12, then PR weeks 13 to 48. Stopping rules: Stop all drugs if HCV RNA ≥ 25 IU/mL at week 4. Stop PR therapy if HCV RNA detectable at week 12 or 24.
	SOF + PR	SOF 400 mg q.d. + PR	Treatment-naive, or Prior relapse, or Prior partial response, or Prior null response, or cirrhotic: SOF + PR weeks 1 to 12.
	SOF + RBV	SOF 400 mg q.d. + weight-based RBV[a]	12 weeks SOF + RBV for 24 weeks can be considered as a therapeutic option for treatment-naive and non-cirrhotic. Treatment-experienced G1 patients who are ineligible to receive an interferon-based regimen.
	SIM + SOF	SIM 150 mg q.d. + SOF 400 mg q.d.	12 weeks of SIM with SOF[b] in patients who are treatment-naive, prior relapse patients, and prior non-responder[c] patients (including partial and null responders) with or without cirrhosis.
	SIM + SOF + RBV	SIM 150 mg q.d. + SOF 400 mg q.d. + Weight-based RBV[a]	All 12 weeks

GENOTYPE	INTERVENTION	DOSE	DURATION
	SOF/LED	SOF 400 mg/LED 90 mg q.d.	12[d] weeks in treatment-naive[e] G1 patients without cirrhosis 12 weeks in treatment-naive[e] G1 patients with cirrhosis[f] 12 weeks in treatment-experienced[g] G1 patients without cirrhosis 24 weeks in treatment-experienced[g] G1 patients with cirrhosis.
	SOF/LED + RBV	SOF 400 mg/LED 90 mg q.d. + weight-based RBV[a]	8,12, or 24 weeks
	PAR/RIT/OMB + DAS	PAR 75 mg/RIT 50 mg/OMB 12.5 mg (two tablets q.d.) + DAS 250 mg b.i.d.	G1b without cirrhosis = 12 weeks
	PAR/RIT/OMB + DAS + RBV	PAR 75 mg/RIT 50 mg/OMB 12.5 mg (two tablets q.d.) + DAS 250 mg b.i.d. + weight-based RBV[a]	G1a without cirrhosis = 12 weeks
	PAR/RIT/OMB + DAS + RBV	PAR 75 mg/RIT 50 mg/OMB 12.5 mg (two tablets q.d.) + DAS 250 mg b.i.d. + weight-based RBV[a]	12 weeks for patients with cirrhosis or 24 weeks for G1a with cirrhosis and prior null response to PR
	DAC + ASU	DAC 60 mg q.d. + ASU 100 mg b.i.d.	G1b = 24 weeks
	DAC + ASU + PEG and RBV	DAC 60 mg q.d. + ASU 100 mg b.i.d. + PEG 180 mcg weekly + weight-based RBV[a]	24 weeks
	DAC + SOF	DAC 60 mg q.d. + SOF 400 mg q.d.	12 weeks
	GRA + ELB	GRA 100 mg q.d. + ELB 20 or 50 mg q.d.	8, 12, or 18 weeks
	GRA + ELB + RBV	GRA 100 mg q.d. + ELB 20 or 50 mg q.d. + weight-based RBV[a]	8, 12, or 18 weeks
	DAC/ASU/BEC + RBV	DAC 30 mg/ASU 200 mg /BEC 75 mg b.i.d. + RBV 200 mg b.i.d.	12 weeks
	DAC/ASU/BEC	DAC 30 mg/ASU 200 mg/BEC 75 mg b.i.d.	12 weeks
	SOF + GS-5816	SOF 400 mg q.d. + GS-5816 25 mg q.d. or GS-5816 100 mg q.d.	8 or 12 weeks
	SOF + GS-5816 + RBV	SOF 400 mg q.d. + GS-5816 25 mg q.d. or GS-5816 100 mg q.d. + RBV (1,000 to 1,200 mg daily)	8 weeks
Genotype 2	Pegylated interferon alfa-2a + RBV (PR)	Pegylated interferon alfa-2a 180 mcg once weekly + weight-based RBV if < 75 kg = 1,000 mg if ≥ 75 kg = 1,200 mg each day in two divided doses	24 to 48 weeks

GENOTYPE	INTERVENTION	DOSE	DURATION
	Pegylated interferon alfa-2b + RBV (PR)	Pegylated interferon alfa-2b 1.5 mcg per kg once weekly + weight-based RBV (800 mg to 1,400 mg) each day in two divided doses	24 to 48 weeks
	SOF + RBV	SOF 400 mg + weight-based RBV[a]	12 weeks Or 16 weeks for treatment-experienced patients who are cirrhotic.
	SOF + PR	SOF 400 mg q.d. + PR	Treatment-naive, or Prior relapse, or Prior partial response, or Prior null response, or Cirrhotic: SOF + PR weeks 1 to 12
	DAC + SOF	DAC 30 q.d. or DAC 60 mg q.d. + SOF 400 mg q.d.	12 weeks
	GRA + ELB + RBV	GRA 100 mg q.d. + ELB 50 mg q.d. + weight-based RBV[a]	12 weeks
	SOF + GS-5816	SOF 400 mg q.d. + GS-5816 25 mg q.d. or GS-5816 100 mg q.d.	8 or 12 weeks
	SOF + GS-5816 + RBV	SOF 400 mg q.d. + GS-5816 25 mg q.d. or GS-5816 100 mg q.d. + RBV 1,000 mg daily	8 weeks
Genotype 3	Pegylated interferon alfa-2a + RBV (PR)	Pegylated interferon alfa-2a 180 mcg once weekly + weight-based RBV if < 75 kg = 1,000 mg if ≥ 75 kg = 1,200 mg each day in two divided doses	24 to 48 weeks
	Pegylated interferon alfa-2b + RBV (PR)	Pegylated interferon alfa-2b 1.5 mcg per kg once weekly + weight-based RBV (800 mg to 1,400 mg) each day in two divided doses	24 to 48 weeks
	SOF + RBV	SOF 400 mg q.d. + weight-based RBV[a]	24 weeks
	SOF + PR	SOF 400 mg q.d. + PR	Treatment-naive, or Prior relapse, or Prior partial response, or Prior null response, or Cirrhotic: SOF + PR weeks 1 to 12
	SOF/LED + RBV	SOF 400 mg/LED 90 mg q.d. + weight-based RBV[a]	At least 8 weeks
	DAC + SOF	DAC 60 mg q.d. + SOF 400 mg q.d.	12 or 24 weeks
	SOF + GS-5816	SOF 400 mg q.d. + GS-5816 25 mg q.d. or GS-5816 100 mg q.d.	12 weeks
	PAR/RIT + ABT-530 + RBV	NR	12 weeks
	PAR/RIT + ABT-530	NR	12 weeks

GENOTYPE	INTERVENTION	DOSE	DURATION
Genotype 4	Pegylated interferon alfa-2a + RBV (PR)	Pegylated interferon alfa-2a 180 mcg once weekly + weight-based RBV if < 75 kg = 1,000 mg if ≥ 75 kg = 1,200 mg each day in two divided doses	Up to 48 weeks
	Pegylated interferon alfa-2b + RBV (PR)	Pegylated interferon alfa-2b 1.5 mcg per kg once weekly + weight-based RBV (800 mg to 1,400 mg) each day in two divided doses	Up to 48 weeks
	SOF + PR	SOF 400 mg q.d. + PR	Treatment-naive, or Prior relapse, or Prior partial response, or Prior null response, or Cirrhotic: SOF + PR weeks 1 to 12
	SOF + RBV	SOF 400 mg q.d. + weight-based RBV[a]	12 weeks or 24 weeks
	SOF/LED	SOF 400 mg/LED 90 mg q.d.	12 weeks
	GRA + ELB + RBV	GRA 100 mg q.d. + ELB 50 mg q.d. + weight-based RBV[a]	12 weeks
	SOF + GS-5816	SOF 400 mg q.d. + GS-5816 25 mg q.d. or GS-5816 100 mg q.d.	12 weeks
	DAC + ASU + PEG and RBV	DAC 60 mg q.d. + ASU 100 mg b.i.d. + PEG 180 mcg weekly + weight-based RBV[a]	24 weeks
	DAC/ASU/BEC	DAC 30 mg/ASU 200 mg/BEC 75 mg b.i.d.	12 weeks
	DAC/ASU/BEC	DAC 30 mg/ASU 200 mg/BEC 150 mg b.i.d.	12 weeks
Genotype 5	Pegylated interferon alfa-2a + RBV (PR)	Pegylated interferon alfa-2a 180 mcg once weekly + weight-based RBV if < 75 kg = 1,000 mg if ≥ 75 kg = 1,200 mg each day in two divided doses	Up to 48 weeks
	Pegylated interferon alfa-2b + RBV (PR)	Pegylated interferon alfa-2b 1.5 mcg per kg once weekly + weight-based RBV (800 mg to 1,400 mg) each day in two divided doses	Up to 48 weeks
	SOF + PR	SOF 400 mg q.d. + PR	Treatment-naive, or Prior relapse, or Prior partial response, or Prior null response, or Cirrhotic: SOF + PR weeks 1 to 12
	DAC + SOF	NR	At least 8 weeks
	SOF + GS-5816	SOF 400 mg q.d. + GS-5816 25 mg q.d. or GS-5816 100 mg q.d.	At least 8 weeks

GENOTYPE	INTERVENTION	DOSE	DURATION
	GRA + ELB + RBV	GRA 100 mg q.d. + ELB 50 mg q.d. + weight-based RBV[a]	12 weeks
Genotype 6	SOF + PR	SOF 400 mg q.d.+ PR	Treatment-naive, or Prior relapse, or Prior partial response, or Prior null response, or Cirrhotic: SOF + PR weeks 1 to 12
	DAC + SOF		At least 8 weeks
	SOF/LED	SOF 400 mg/LED 90 mg q.d.	12 weeks
	SOF + GS-5816	SOF 400 mg q.d. + GS-5816 25 mg q.d. or GS-5816 100 mg q.d.	12 weeks
	GRA + ELB + RBV	GRA 100 mg q.d. + ELB 50 mg q.d. + weight-based RBV[a]	12 weeks

ASU = asunaprevir; BEC = beclabuvir; b.i.d. = twice daily; BOC = boceprevir; DAC = daclatasvir; DAS = dasabuvir; ELB = elbasvir; G1 = genotype 1; GRA = grazoprevir; HCV RNA = hepatitis C virus ribonucleic acid; IU = international unit; LED = ledipasvir; NR = not reported; OMB = ombitasvir; PAR = paritaprevir; PEG = pegylated interferon alfa; PR = pegylated interferon alfa combined with ribavirin; q.d. = once daily; RBV = ribavirin; RIT = ritonavir; SIM = simeprevir; SOF = sofosbuvir; TEL = telaprevir; t.i.d. = three times daily.

[a] Weight-based RBV dosing is < 75 kg = 1,000 mg daily or ≥ 75 kg = 1,200 mg daily, administered orally in two divided doses.

[b] Treatment for up to 24 weeks' duration should be considered in patients with cirrhosis.

[c] Prior relapser or non-responder; following prior treatment with interferon (pegylated or non-pegylated), with or without RBV.

[d] SOF/LED for 8 weeks can be considered in treatment-naive patients without cirrhosis who have pre-treatment HCV RNA less than 6 million IU/mL.

[e] Treatment-naive is defined as no prior exposure to any interferon, RBV, or other approved or experimental HCV-specific direct-acting antiviral agent at the time of treatment initiation.

[f] Cirrhosis is defined as any one of the following: Liver biopsy showing cirrhosis (e.g., Metavir score = 4 or Ishak score ≥ 5); or Fibroscan (in countries where locally approved) showing cirrhosis or results > 12.5 kPa; or FibroTest score of > 0.75 and an aspartate aminotransferase (AST):platelet ratio index (APRI) of > 2.

[g] Treatment-experienced is defined as those who failed prior therapy with an interferon-based regimen, including regimens containing an HCV protease inhibitor.