

5.11 PARITAPREVIR 75MG, RITONAVIR 50MG, OMBITASVIR 12.5MG AND DASABUVIR 250MG +/- RIBAVIRIN 200MG/600MG TABLETS, Viekira PAK / Viekira PAK-RBV®, AbbVie Pty Ltd

The co-packaged fixed dose combination of paritaprevir/ritonavir/ombitasvir plus dasabuvir with or without ribavirin is referred to as Viekira PAK / Viekira PAK-RBV in the PBAC minutes.

1 Purpose of Application

1.1 The submission requested a Section 85 Authority Required (STREAMLINED) listing for Viekira PAK / Viekira PAK-RBV to treat patients with genotype 1 chronic hepatitis C (CHC) infection who have compensated liver disease, irrespective of previous treatment history.

2 Requested listing

2.1 The requested listings are:

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
PARITAPREVIR/RITONAVIR/OMBITASVIR Tablet 75mg/50mg/12.5mg	56			
DASABUVIR Tablet 250mg	56	2	\$ [REDACTED]	Viekira PAK® AbbVie Pty Ltd
PARITAPREVIR/RITONAVIR/OMBITASVIR Tablet 75mg/50mg/12.5mg	56			
DASABUVIR Tablet 250mg	56	2	\$ [REDACTED]	Viekira PAK-RBV® AbbVie Pty Ltd
RIBAVIRIN Tablet 200mg	168			
PARITAPREVIR/RITONAVIR/OMBITASVIR Tablet 75mg/50mg/12.5mg	56			
DASABUVIR Tablet 250mg	56	2	\$ [REDACTED]	Viekira PAK-RBV® AbbVie Pty Ltd
RIBAVIRIN Tablet 600mg	56			
PARITAPREVIR/RITONAVIR/OMBITASVIR Tablet 75mg/50mg/12.5mg	56			
DASABUVIR Tablet 250mg	56	5	\$ [REDACTED]	Viekira PAK-RBV® AbbVie Pty Ltd
RIBAVIRIN Tablet 200mg	168			
PARITAPREVIR/RITONAVIR/OMBITASVIR Tablet 75mg/50mg/12.5mg	56	5	\$ [REDACTED]	Viekira PAK- AbbVie Pty Ltd

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DASABUVIR Tablet 250mg	56	RBV®
RIBAVIRIN Tablet 600mg	56	

Section 85 Authority required (STREAMLINED)

Chronic Hepatitis C, Genotype 1b, without cirrhosis: Viekira PAK 12 weeks	
Clinical criteria	Patient must have compensated disease; Patient must not have cirrhosis; The treatment must be limited to a maximum duration of 12 weeks.
Population criteria	Patient must be 18 years or older;
Treatment Criteria:	Must be treated in an accredited treatment centre; Evidence of chronic genotype 1b infection (repeatedly anti-HCV positive and HCV RNA positive) must be documented in the patient's medical records.
Chronic Hepatitis C, Genotype 1a, without cirrhosis, Genotype 1a and 1b with cirrhosis (except 1a patients will null response to prior treatment): Viekira PAK-RBV 12 weeks	
Clinical criteria	Patient must have compensated disease; Patients with genotype 1a and compensated cirrhosis must be treatment naïve or if previously treated, had a partial response or relapse to prior therapy for GT1 CHC; Patients with genotype 1b must have compensated cirrhosis; The treatment must be limited to a maximum duration of 12 weeks; The treatment must be in combination with ribavirin.
Population criteria	Patient must be 18 years or older; Patient must not be pregnant or breastfeeding. Female partners of male patients must not be pregnant. Patients and their partners must each be using an effective form of contraception if of child-bearing age.
Treatment Criteria:	Must be treated in an accredited treatment centre; Evidence of chronic genotype 1a/1b infection (repeatedly anti-HCV positive and HCV RNA positive) must be documented in the patient's medical records.
Chronic hepatitis C, Genotype 1a with cirrhosis, with null response to prior treatment: Viekira PAK-RBV 24 weeks	
Clinical criteria	Patient must have compensated disease; Patient must have cirrhosis; Patient must have had a null response to prior therapy for GT1 CHC; The treatment must be limited to a maximum duration of 24 weeks.
Population criteria	Patient must be 18 years or older; Patient must not be pregnant or breastfeeding. Female partners of male patients must not be pregnant. Patients and their partners must each be using an effective form of contraception if of child-bearing age.
Treatment Criteria:	Must be treated in an accredited treatment centre; Evidence of chronic genotype 1a infection (repeatedly anti-HCV positive and HCV RNA positive) must be documented in the patient's medical records.

GT = genotype; CHC = chronic hepatitis C; HCV = hepatitis C; RNA = ribonucleic acid

Note:

- [REDACTED]
- 2.2 There are two proposed Viekira PAK-RBV preparations. One contains 56 x 600mg ribavirin tablets, and is used for patients ≥ 75 kg who require 1,200mg of ribavirin per day. Another contains 168 x 200mg ribavirin tablets, which is used for patients who are <75 kg and require 1,000mg of ribavirin per day although there are sufficient tablets for patients who are ≥ 75 kg. Patients who are <75 kg only require 140 tablets of 200mg for 28 days, therefore there will be 28 tablets left over. Patients will need to be made aware that there will be surplus tablets. Alternative preparations were discussed in the proposed product information and would reduce pill burden and avoid surplus tablets. The PSCR stated 'Ribavirin is co-packaged and will be supplied in the first instance in bottles of 168 X 200mg tablets or 56 X 600mg tablets'.
 - 2.3 The requested listing did not preclude treatment for patients who are co-infected with either hepatitis B virus (HBV) or human immunodeficiency virus (HIV). There was no clinical evidence provided to determine the impact of Viekira PAK / Viekira PAK-RBV in patients with these co-infections. The PSCR provided data from a randomised open label study (Turquoise I) evaluating Viekira PAK-RBV in HCV/HIV-1 co-infected adults, with and without cirrhosis, for 12 or 24 weeks and claimed that overall efficacy and safety observed in this study are consistent with that observed in non-co-infected subjects. The ESC noted that the current listings for CHC do not specifically exclude use in co-infected patients.
 - 2.4 At its March 2015 meeting, the PBAC recommended the listing of other treatments for CHC. During its consideration, the PBAC requested that the Department consult with clinical experts on certain aspects of the restriction. It would be expected that the listing of this treatment would be similar to the listing of other interferon-free treatments, which is yet to be finalised.
 - 2.5 Listing was sought on the basis that Viekira PAK / Viekira PAK-RBV was cost-effective in comparison with 'no treatment' or a 'protease inhibitor plus PR'.

For more detail on PBAC's view, see section 7 "PBAC outcome"

3 Background

- 3.1 The submission was made under the TGA/PBAC Parallel Process. The regulatory submission has a positive TGA Delegate’s Overview and was considered at the 304th ACPM meeting on 5 June 2015.
- 3.2 This was the first submission of Viekira PAK / Viekira PAK-RBV to the PBAC for the treatment of genotype 1 CHC.

4 Clinical place for the proposed therapy

- 4.1 HCV infection is a major cause of chronic liver disease. The cycle of viral reproduction within hepatic cells and the response by the host immune system to the infection results in damage to the host’s liver. Chronic infection can lead to scarring of the liver and ultimately to cirrhosis. In some cases, patients with liver cirrhosis develop liver failure, liver cancer or life-threatening oesophageal and gastric varices. Currently, genotype 1 accounts for 49-55% of infections in Australia.
- 4.2 DAAs, including boceprevir, telaprevir and simeprevir (HCV NS3/4A protease inhibitors) are currently reimbursed on the PBS for the treatment of genotype 1 CHC. The current listing of these protease inhibitors requires that they be used in combination with peginterferon and ribavirin (PR).
- 4.3 Sofosbuvir (SOF) in combination with PR, ledipasvir/sofosbuvir (LDV/SOF) fixed dose combination, daclatasvir in combination with sofosbuvir (DCV+SOF) were recommended at the March 2015 PBAC meeting for the treatment of genotype 1 CHC.
- 4.4 Paritaprevir is a protease inhibitor. Although ritonavir is also a protease inhibitor, at the doses used in the fixed-dose combination it acts as a pharmacokinetic enhancer that increases peak and trough plasma drug concentrations of paritaprevir and increases overall drug exposure. Ombitasvir is an inhibitor of HCV NS5A. Dasabuvir is a non-nucleoside inhibitor of the HCV RNA-dependent RNA polymerase encoded by the NS5B gene. Ribavirin is a synthetic nucleoside analogue that shows *in vitro* activity against some RNA and DNA viruses. Thus, Viekira PAK / Viekira PAK–RBV each include several DAAs with distinct mechanisms of action to target HCV at multiple steps in the viral lifecycle. Viekira PAK / Viekira PAK–RBV and other DAAs which are listed or recently considered by the PBAC are shown below.

Table 1: Mechanism of Actions of DAAs

	NS3/4A protease inhibitor	NS5A inhibitor	NS5B polymerase inhibitor	Other
Viekira PAK Viekira PAK-RBV	Paritaprevir	Ombitasvir	Dasabuvir (Non-nucleoside inhibitor)	Ritonavir (pharmacokinetic enhancer) Ribavirin
Other DAAs	Boceprevir Telaprevir Simeprevir Asunaprevir	Ledipasvir Daclatasvir	Sofosbuvir (Nucleotide analogue inhibitor)	Ribavirin

- 4.5 The duration of therapy and addition of ribavirin are dependent on the patient population. In Section E of the submission, in year 1 of listing ███% of patients was assumed to be treated with 24 weeks of Viekira PAK–RBV, which decreased to ███% in year 5 as this pool of previously treated patients are treated. Currently, the American Association for the Study of Liver Disease (AASLD) guidelines recommends a broader population of patients be treated with 24 weeks of Viekira PAK–RBV than Genotype 1a, with cirrhosis, with null response to prior treatment.

Table 2: Dosing and duration of treatment with Viekira PAK / Viekira PAK-RBV

Population	Treatment, packs and duration	Dosing	Ribavirin dosing
Genotype 1b, non-cirrhotic	Viekira PAK 1 pack + 2 repeats 12 weeks	2 x OMB/PAR/r (12.5/75/50mg) in the morning with food	Nil
Genotype 1a, with or without cirrhosis ^b Genotype 1b, with cirrhosis	Viekira PAK-RBV 1 pack + 2 repeats 12 weeks	1 x DSV (250mg) in the morning with food and 1 x DSV (250mg) in the evening with food.	For patients <75kg 3 x 200mg tablets in the morning and 2 x 200mg tablets in the evening For patients ≥75kg 1 x 600mg tablet in the morning and 1 x 600mg tablet in the evening ^a
Genotype 1a, with cirrhosis, with null response to prior treatment	Viekira PAK-RBV 1 pack + 5 repeats 24 weeks		

^aThe submission proposes that patients could take 3x200mg morning and evening for patients ≥75kg. There are sufficient tablets (168) in the 200mg ribavirin preparation to permit this.

^bExcept cirrhotic patients who are null responders to previous treatment.

OMB = ombitasvir; PAR = paritaprevir; r = ritonavir; DSV = dasabuvir; RBV = ribavirin.

Source: Table A-4, p55 of the submission

For more detail on PBAC's view, see section 7 "PBAC outcome"

5 Comparator

- 5.1 The submission presented a number of comparisons of Viekira PAK / Viekira PAK-RBV versus:
- Telaprevir plus PR (based on two head-to-head randomised controlled trials (RCTs))
 - No treatment (based on two placebo controlled RCTs)
 - Simeprevir (SMV) plus PR (indirect comparison)
 - LDV/SOF (indirect comparison)
 - SOF+PR (indirect comparison)
 - DCV+SOF (indirect comparison)
 - Daclatasvir in combination with asunaprevir (indirect comparison).
- 5.2 As many patients have not been receiving active treatment while awaiting the emergence of interferon-free treatment regimens (5.17 Sofosbuvir public summary document, paragraph 7.5), the PBAC have previously accepted the appropriate comparator for the majority of patients was 'no treatment'. The PBAC recommended the listing of an all-oral, interferon-free treatment regimen for genotype 1 HCV infection (LDV/SOF) at the March 2015 PBAC meeting. It is likely that the interferon-free regimens will become the standard of care and can be considered an appropriate comparator. Therefore, the *evaluation* focused on the comparison of

Viekira PAK / Viekira PAK-RBV with ‘no treatment’ and ‘LDV/SOF’ *in the clinical evaluation*. The ESC noted that this approach was consistent with previous PBAC considerations.

- 5.3 The PSCR reasserted the choice of comparators presented in the submission.

For more detail on PBAC’s view, see section 7 “PBAC outcome”

6 Consideration of the evidence

Sponsor hearing

- 6.1 The sponsor requested a hearing for this item.
- 6.2 The clinical expert addressed the clinical positioning of and the number of patients seeking treatment with Viekira PAK / Viekira PAK-RBV and other IFN-free treatments in the treatment algorithm of genotype 1 HCV infection. When questioned by PBAC about the effect of pill burden and adherence to treatment, the clinical expert considered it unlikely to be a major issue given the high treatment effectiveness and benefit of Viekira PAK / Viekira PAK-RBV and the short treatment duration. The expert did note that there may be a preference for regimens requiring a lower number of pills and that the availability of a range of treatment options would provide choice for clinicians and patients and allow individualisation of treatment. When questioned by PBAC about the rate of transition to cirrhosis, the clinical expert expressed that fibrosis stage in reality was same as seen in clinical trials sourced from tertiary liver clinics.
- 6.3 The PBAC considered that the hearing gave a clinical and epidemiological perspective of patient treatment but did not add substantively to the evidence presented in the submission

Consumer comments

- 6.4 The PBAC noted and welcomed the input from individuals (114), health care professionals (14) and organisations (17) via the Consumer Comments facility on the PBS website. The large number of comments and discussion reiterate the comments received during previous considerations of the IFN-free treatments, namely the benefit of the availability of a highly effective treatment that should be made available for all infected individuals, the improved quality of life as well as the side effects avoided associated with the current treatments.
- 6.5 The PBAC recalled the discussion during meeting of the representatives of the PBAC with Hepatitis Australia, Hepatitis NSW, the Australian Injecting and the Illicit Drug User’s League prior to the March 2015 PBAC meeting.
- 6.6 The PBAC noted and welcomed this input.

Clinical trials

- 6.7 The evidence used in the submission to compare Viekira PAK / Viekira PAK-RBV versus no treatment was several placebo-controlled trials. The evaluation extracted

sustained virologic response (SVR) rates from single arms of trials that used the correct regimen of Viekira PAK / Viekira PAK-RBV for analysis, as patients receiving no treatment do not achieve SVR, and therefore, trials including a comparator arm of placebo should provide the same incremental estimate of SVR as a single arm of a study against an assumed SVR rate of zero.

6.8 The comparison of Viekira PAK / Viekira PAK-RBV versus LDV/SOF in the submission was based on unadjusted indirect comparison of single arms of individual studies.

6.9 Details of the studies presented in the submission are provided in the table below.

Table 3: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Trials involving Viekira PAK / Viekira PAK-RBV		
Malachite I	A randomized, open-label study to evaluate the efficacy and safety of ABT-450/ritonavir/ABT-267 and ABT-333 co-administered with and without ribavirin compared to telaprevir co-administered with pegylated interferon α -2a and ribavirin in treatment-naïve adults with chronic hepatitis C genotype 1 virus infection (MALACHITE I)	Primary Analysis CSR (no report date) 2015
Malachite II	A randomized, open-labelled study to evaluate the efficacy and safety of ABT-450/ritonavir/ABT-267 and ABT-333 co-administered with ribavirin compared to telaprevir co-administered with pegylated interferon α -2a and ribavirin in treatment-experienced adults with chronic hepatitis C genotype 1 virus infection (MALACHITE-II).	Primary Analysis CSR (no report date) 2015
Turquoise II Poordad et al 2014	A randomized, open-label study to evaluate the safety and efficacy of ABT-450/ritonavir/ABT-267 (ABT-450/r/ABT-267) and ABT-333 co-administered with ribavirin (RBV) in adults with genotype 1 chronic hepatitis C virus (HCV) infection and cirrhosis (TURQUOISE-II).	Primary Analysis CSR 1 April 2014
	Primary publication Poordad, F., C. Hezode, R. Trinh, K. V. Kowdley, S. Zeuzem, K. Agarwal, M. L. Shiffman, H. Wedemeyer, T. Berg, E. M. Yoshida, X. Forns, S. S. Lovell, B. Da Silva-Tillmann, C. A. Collins, A. L. Campbell, T. Podsadecki and B. Bernstein ⁷ . "ABT-450/r-ombitasvir and dasabuvir with ribavirin for hepatitis C with cirrhosis."	2014 New England Journal of Medicine 370 (21): 1973-1982 ⁶
	F. Poordad, C. Hezode, R. Trinh, K.V. Kowdley, S. Zeuzem, K. Agarwal, M.L. Shiffman, H. Wedemeyer, T. Berg, E.M. Yoshida, X. Forns, S.S. Lovell, B. Da Silva-Tillmann, A.L. Campbell and T. Podsadecki ⁸ . SVR12 rates of 92–96% in 380 hepatitis C virus genotype 1-infected adults with compensated cirrhosis treated with ABT-450/r/ABT-267 and ABT-333 plus ribavirin (3D+RBV).	2014 Journal of Hepatology 60 (1) Supplement S523 ⁹ . This abstract was also presented in Gastroenterology (Kowdley et al 2014) ¹⁰
Sapphire I Feld et al 2014	A randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of ABT-450/ritonavir/ABT-267 (ABT-450/r/ABT-267) and ABT-333 co-administered with ribavirin (RBV) in treatment-naïve adults with genotype 1 chronic hepatitis C virus (HCV) infection (SAPPHIRE-I).	Primary Analysis CSR 21 February 2014
	Primary publication Feld, J. J., K. V. Kowdley, E. Coakley, S. Sigal, D. R. Nelson, D. Crawford, O. Weiland, H. Aguilar, J. Xiong, T. Pilot-Matias, B. DaSilva-Tillmann, L. Larsen, T. Podsadecki and B. Bernstein ¹² . "Treatment of HCV with ABT-450/r-ombitasvir and dasabuvir with	2014 New England Journal of Medicine 370 (17): 1594-1603 ¹¹

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	ribavirin."	
	J.J. Feld, K.V. Kowdley, E. Coakley, S. Sigal, D. Nelson, D. Crawford, O. Weiland, H. Aguilar, J. Xiong, B. DaSilva-Tillmann, L. Larsen and T. Podsadecki ¹³ . Phase 3 placebo-controlled study of interferon-free 12-week regimen of ABT-450/r/ABT-267 ABT-333 and ribavirin in 631 treatment-naive adults with hepatitis C virus genotype 1.	2014 Journal of Hepatology 60 (1) Supplement S25 ¹⁴
Sapphire II Zeuzem et al 2014	A randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of ABT-450/ritonavir/ABT-267 (ABT-450/r/ABT-267) and ABT-333 co-administered with ribavirin (RBV) in treatment-experienced adults with genotype 1 chronic hepatitis C virus (HCV) infection (SAPPHIRE-II).	Primary Analysis CSR 18 February 2014
	Primary publication Zeuzem, S., I. M. Jacobson, T. Baykal, R. T. Marinho, F. Poordad, M. Bourliere, M. S. Sulkowski, H. Wedemeyer, E. Tam, P. Desmond, D. M. Jensen, A. M. Di Bisceglie, P. Varunok, T. Hassanein, J. Xiong, T. Pilot-Matias, B. DaSilva-Tillmann, L. Larsen, T. Podsadecki and B. Bernstein ¹⁶ "Retreatment of HCV with ABT-450/r-ombitasvir and dasabuvir with ribavirin."	2014 N Engl J Med 370(17): 1604-1614 ¹⁵
	Ira M. Jacobson, Stefan Zeuzem, Tolga Baykal, Rui T. Marinho, Fred Poordad, Marc Bourliere, Mark Sulkowski, Heiner Wedemeyer, Edward Tam, Paul V. Desmond, Donald M. Jensen, Adrian M. Di Bisceglie, Peter Varunok, Tarek Hassanein, Junyuan Xiong, Barbara DaSilva-Tillmann, Lois Larsen and Thomas Podsadecki ¹⁷ . Phase 3 placebo-controlled study of interferon-free 12-week regimen of ABT-450/r/ABT-267 ABT-333 and ribavirin in 394 treatment-experienced adults with hepatitis C virus genotype 1.	2014 Gastroenterology 146 (5) Supplement 1 S-904 ¹⁸ . This abstract was also presented in Journal of Hepatology ¹⁹
Pearl II Andreone et al 2014	A randomized, open-label, multicenter study to evaluate the safety and antiviral activity of the combination of ABT-450/ritonavir/ABT-267 (ABT-450/r/ABT-267) and ABT-333 with and without ribavirin in treatment-experienced subjects with genotype 1b chronic hepatitis C virus (HCV) infection (PEARL-II).	Primary Analysis CSR 2 April 2014
	Primary publication Andreone, P., M. G. Colombo, J. V. Enejosa, I. Koxsal, P. Ferenci, A. Maieron, B. Mullhaupt, Y. Horsmans, O. Weiland, H. W. Reesink, L. Rodrigues, Jr., Y. B. Hu, T. Podsadecki and B. Bernstein ²⁰ . "ABT-450, ritonavir, ombitasvir, and dasabuvir achieves 97% and 100% sustained virologic response with or without ribavirin in treatment-experienced patients with HCV genotype 1b infection."	2014 Gastroenterology 147(2): 359-365 e351 ²⁰
	Pietro Andreone, Massimo Colombo, Jeffrey V. Enejosa, Iftihar Koxsal, Peter Ferenci, Andreas Maieron, Beat Müllhaupt, Yves Horsmans, Ola Weiland, Henk W. Reesink, Lino Rodrigues Jr, Yiran B. Hu and Thomas Podsadecki ²¹ . Randomized phase 3 trial of interferon-free 12-week regimen of ABT-450/r/ABT-267 ABT-333 with or without ribavirin in hepatitis C virus genotype 1b-infected treatment-experienced patients.	2014 Gastroenterology 146 (5) Supplement 1 S-159 ²²
Pearl III Ferenci et al 2014	A randomized, double-blind, controlled study to evaluate the efficacy and safety of the combination of ABT-450/ritonavir/ABT-267 (ABT-450/r/ABT-267) and ABT-333 with and without ribavirin (RBV) in treatment-naïve adults with genotype 1b chronic hepatitis C virus (HCV) infection (PEARL-III).	Primary Analysis CSR 27 March 2014
	Primary publication (Pearl III and Pearl IV) Ferenci, P., D. Bernstein, J. Lalezari, D. Cohen, Y. Luo, C.	2014 New England Journal of

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	Cooper, E. Tam, R. T. Marinho, N. Tsai, A. Nyberg, T. D. Box, Z. Younes, P. Enayati, S. Green, Y. Baruch, B. R. Bhandari, F. A. Caruntu, T. Sepe, V. Chulanov, E. Janczewska, G. Rizzardini, J. Gervain, R. Planas, C. Moreno, T. Hassanein, W. Xie, M. King, T. Podsadecki and K. R. Reddy (2014). "ABT-450/r-ombitasvir and dasabuvir with or without ribavirin for HCV."	Medicine 370(21): 1983-1992. ²³
	P. Ferenci, A. Nyberg, P. Enayati, D. Bernstein, Y. Baruch, F.A. Caruntu, V. Chulanov, E. Janczewska, Z. Younes, R.T. Marinho, G. Rizzardini, J. Gervain, R. Planas, C. Moreno, W. Xie, D. Cohen, M. King, T. Podsadecki and K.R. Reddy 2014. 12 weeks of ABT-450/r/267 + ABT-333 achieved SVR in 99% of 419 treatment-naïve HCV genotype 1b-infected adults with or without ribavirin.	2014 Journal of Hepatology 60 (1) Supplement S527 ²⁴
Pearl IV Ferenci et al 2014	A randomized, double-blind, controlled study to evaluate the efficacy and safety of the combination of ABT-450/ritonavir/ABT-267 (ABT-450/r/ABT-267) and ABT-333 with and without ribavirin (RBV) in treatment-naïve adults with genotype 1a chronic hepatitis C virus (HCV) infection (PEARL-IV).	Primary Analysis CSR 26 March 2014
	Primary publication (see Pearl III) David Bernstein, Jacob Lalezari, Yan Luo, Terry D. Box, Ziad H. Younes, Sinikka Green, Bai R. Bhandari, Thomas Sepe, Curtis Cooper, Edward Tam, Naoky Tsai, Tarek Hassanein, Wangang Xie and Thomas Podsadecki ²⁵ . A 12-week regimen of ABT-450/r/ABT-267 and ABT-333 with or without ribavirin achieves SVR12 rates of 90% in treatment-naïve adults infected with hepatitis C virus genotype 1a.	2014 Gastroenterology 146 5 Supplement 1 S-977-S-978 ²⁶
Trials involving ledipasvir+sofosbuvir		
ION-1 Afdhal et al 2014	Primary publication Afdhal, N., S. Zeuzem, P. Kwo, M. Chojkier, N. Gitlin, M. Puoti, M. Romero-Gomez, J. P. Zarski, K. Agarwal, P. Buggisch, G. R. Foster, N. Brau, M. Buti, I. M. Jacobson, G. M. Subramanian, X. Ding, H. Mo, J. C. Yang, P. S. Pang, W. T. Symonds, J. G. McHutchison, A. J. Muir, A. Mangia, P. Marcellin and I. O. N. Investigators ²⁸ . "Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection."	2014 N Engl J Med 370(20): 1889-1898. ²⁷
	A. Mangia, P. Marcellin, P. Kwo, G.R. Foster, M. Buti, N. Bräu, A. Muir, J.C. Yang, H. Mo, X. Ding, P.S. Pang, W.T. Symonds, J.G. McHutchison, S. Zeuzem and N. Afdhal ²⁹ . All oral fixed-dose combination sofosbuvir/ledipasvir with or without ribavirin for 12 or 24 weeks in treatment-naïve genotype 1 HCV-infected patients: the phase 3 ION-1 study.	2014 Journal of Hepatology 60 1 Supplement S523 - S524. ³⁰ This abstract was also presented in Gastroenterology ³¹
	Z. Younossi, M. Stepanova, P. Marcellin, N. Afdhal, F. Nader and S. Hunt ³² . Ledipasvir (LDV) and sofosbuvir (SOF) combination improves patient-reported outcomes (PRO) during treatment of chronic hepatitis C (CH-C) patients: results from the ION-1 clinical trial.	2014 Journal of Hepatology 60 1 Supplement S536 - S537. ³²
ION-2 Afdhal et al 2014	Primary publication Afdhal, N., K. R. Reddy, D. R. Nelson, E. Lawitz, S. C. Gordon, E. Schiff, R. Nahass, R. Ghalib, N. Gitlin, R. Herring, J. Lalezari, Z. H. Younes, P. J. Pockros, A. M. Di Bisceglie, S. Arora, G. M. Subramanian, Y. Zhu, H. Dvory-Sobol, J. C. Yang, P. S. Pang, W. T. Symonds, J. G. McHutchison, A. J. Muir, M. Sulkowski, P. Kwo and I. O. N. Investigators ³⁴ . "Ledipasvir and sofosbuvir for previously treated HCV genotype 1 infection."	2014 N Engl J Med 370(16): 1483-1493. ³³
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	Bisceglie, Sanjeev Arora, Jenny C. Yang, Hadas Dvory-Sobol, Yanni Zhu, Phil Pang, William T. Symonds, John G. McHutchison, Mark Sulkowski and Nezam H. Afdhal ³⁵ . All oral fixed-dose combination sofosbuvir/ledipasvir with or without ribavirin for 12 or 24 weeks in treatment-experienced genotype 1 HCV infected patients: the phase 3 ION-2 study.	Supplement 1 S-904. ³⁶ . This abstract was also presented in the Journal of Hepatology ³⁷
ION-3 Kowdley et al 2014	Primary publication Kowdley, K. V., S. C. Gordon, K. R. Reddy, L. Rossaro, D. E. Bernstein, E. Lawitz, M. L. Shiffman, E. Schiff, R. Ghalib, M. Ryan, V. Rustgi, M. Chojkier, R. Herring, A. M. Di Bisceglie, P. J. Pockros, G. M. Subramanian, D. An, E. Svarovskaia, R. H. Hyland, P. S. Pang, W. T. Symonds, J. G. McHutchison, A. J. Muir, D. Pound, M. W. Fried and I. O. N. Investigators ³⁹ . "Ledipasvir and sofosbuvir for 8 or 12 weeks for chronic HCV without cirrhosis."	2014 N Engl J Med 370(20): 1879-1888. ³⁸
	K.V. Kowdley, G.C. Stuart, R.K. Reddy, L. Rossaro, D.E. Bernstein, D. An, E.S. Svarovskaia, R.H. Hyland, P.S. Pang, W.T. Symonds, J.G. Mchutchison, A.J. Muir, P.J. Pockros, D. Pound and M.W. Fried ⁴⁰ . Sofosbuvir/ledipasvir with and without ribavirin for 8 weeks compared to sofosbuvir/ledipasvir for 12 weeks in treatment-naïve non-cirrhotic genotype-1 HCV-infected patients: the phase 3 ION-3 study. Journal of Hepatology 60 1 Supplement S23 - S24.	2014 Journal of Hepatology 60 1 Supplement S23 - S24 ⁴¹ . This abstract was also presented in Gastroenterology ⁴² .

The submission also presented Coral I to assess the efficacy and safety of Viekira PAK / Viekira PAK-RBV for 24 weeks in genotype 1 HCV infected adult liver transplant recipients. This study has been excluded from consideration during the evaluation as this population is not included in the requested PBS listing.

Source: Table B-3, pp104-112 of the submission.

- 6.10 There were eight studies of Viekira PAK / Viekira PAK-RBV, comparing treatment effects either with placebo (Sapphire I, Sapphire II), with or without ribavirin (Pearl III and Pearl IV), with telaprevir plus PR (Malachite I and Malachite II) or they were non-comparative (Turquoise II and Pearl II). All of these studies were treated as non-comparative single arm studies with respect to the estimation of SVR rates. All three LDV/SOF studies have been considered by the PBAC previously. The key features of the included evidence are summarised in the table below.

Table 4: Key features of the included evidence

Trial	N ^b	Design/ duration	Risk of bias ^a	Patient population	Outcome	Use in modelled evaluation ^c
Viekira PAK / Viekira PAK-RBV						
Malachite I	83	Single arm of R, OL 48 weeks	High/low	GT1b treatment-naïve non-cirrhotic	SVR12	Used
	69			GT1a treatment-naïve non-cirrhotic		
Malachite II	19	Single arm of R, OL 48 weeks	High/low	GT1a treatment experienced non-cirrhotic	SVR12	Used
Sapphire I	322	R, DB 48 weeks	High/low	GT1a treatment-naïve non-cirrhotic	SVR12	Not used
Sapphire II	173	R, DB 48 weeks	High/low	GT1a treatment-experienced,	SVR12	Not used

				non-cirrhotic		
Turquoise II	74	Single arm of R, OL 48 weeks	High/low	GT1a treatment-naïve cirrhotic	SVR12	Used
	22			GT1b treatment-naïve cirrhotic		
	26			GT1a treatment-experienced cirrhotic		
	46			GT1b treatment-experienced cirrhotic		
Pearl II	91	Single arm of R, OL 48 weeks	High/low	GT1b treatment-experienced, non-cirrhotic	SVR12	Not used
Pearl III	209	R, DB 48 weeks	High/low	GT1b treatment-naïve non-cirrhotic	SVR12	Not used
Pearl IV	100	R, DB 48 weeks	High/low	GT1a treatment-naïve non-cirrhotic	SVR12	Not used
LDV/SOF						
ION-1 LDV/SOF 12 weeks	34	Single arm of R, OL 12 weeks post treatment	High/unclear	Treatment-naïve cirrhotic	SVR12	N/A
ION-3 LDV/SOF 8 weeks	215	Single arm of R, OL 12 weeks post treatment	High/unclear	Treatment-naïve, non-cirrhotic	SVR12	N/A
ION-2 LDV/SOF 12 weeks	109	Single arm of R, OL 12 weeks post treatment	High/unclear	Treatment-experienced (both non-cirrhotic and cirrhotic)	SVR12	N/A

^a refers to bias associated with indirect comparison between Viekira PAK/Viekira PAK-RBV and LDV/SOF or no treatment. There is a high risk of bias associated with the indirect comparison with LDV/SOF, and low risk of bias versus no treatment.

^b the numbers of patients are for the subgroups with the proposed treatment regimen.

^c During the evaluation, SVR rates in the Viekira PAK / Viekira PAK-RBV arms for the appropriate subgroups from all Viekira PAK / Viekira PAK-RBV studies were pooled and used in the economic model.

LDV/SOF = ledipasvir/sofosbuvir; R = randomised; OL = open label; DB = double blind; GT = genotype SVR = sustained virologic response; NA = not applicable.

Source: Compiled during the evaluation.

- 6.11 The comparison of Viekira PAK / Viekira PAK-RBV vs LDV/SOF was performed by comparing the point estimates of SVR from single arms of studies that lack a common comparator. Comparisons were therefore unadjusted and indirect. Overall, the risk of bias associated with such indirect comparisons was very high because the populations may not have been exchangeable. This meant that there was uncertainty with regard to the magnitude of the differences observed between trial arms. The ESC noted the sponsor's comment in the PSCR that the lack of active or placebo controlled trials of LDV/SOF prohibit adjusted indirect comparisons of this regimen with other regimens.
- 6.12 The comparison of Viekira PAK/Viekira PAK-RBV vs no treatment, in terms of efficacy (SVR) was less likely to be biased, as it could be assumed that the no

treatment arm would not demonstrate SVR. The study populations may not, however, have been representative of the target PBS population. Given the availability of double-blind placebo-controlled trials of Viekira PAK/Viekira PAK-RBV, the uncertainty associated with the assessment of safety, relative to no treatment, was reduced.

Comparative effectiveness

- 6.13 The SVR rates observed from the subgroups with the proposed treatment regimens are summarised below.

Table 5: Sustained virologic response by subgroups for Viekira PAK / Viekira PAK-RBV and LDV/SOF

Population	Regimen	Duration	Evidence	SVR rate n/N % [95% CI] ^c
Treatment naïve, non-cirrhotic				
GT1a	Viekira PAK-RBV	12 weeks	Malachite I (Arm A)	67/69 97.1% [89.9, 99.6]
			Sapphire I (Arm A ^a) ^e	307/322 95.3% [92.4, 97.4]
			Pearl IV (Arm A)	97/100 97% [91.5, 99.4]
GT1b	Viekira PAK	12 weeks	Malachite I (Arm D)	81/83 97.6% [91.6, 99.7]
			Pearl III (Arm B) ^d	209/209 100% [98.3, 100]
GT1a/b ^b	LDV/SOF	12 weeks	ION-1	179/179 100% [98, 100]
		24 weeks	ION-1	181/182 99.5% [97, 100]
		8 weeks	ION-3	202/215 94% [89.9, 96.7]
		12 weeks	ION-3	206/216 95.4% [91.7, 97.8]
Treatment naïve, cirrhotic				
GT1a	Viekira PAK-RBV	12 weeks	Turquoise II (Arm A ^a)	59/64 92.2% [82.7, 97.4]
GT1b		12 weeks	Turquoise II (Arm A ^a)	22/22 100% [84.6, 100]
GT1a/b ^b	LDV/SOF	12 weeks	ION-1	32/33 97% [84.2, 99.9]
		24 weeks	ION-1	31/32 96.9% [83.8, 99.9]
Treatment experienced, non-cirrhotic				
GT1a	Viekira PAK-RBV	12 weeks	Malachite II (Arm A ^a)	19/19 100% [82.4, 100]
			Sapphire II (Arm A ^a)	166/173 96% [91.8, 98.4]
GT1b	Viekira PAK	12 weeks	Pearl II (Arm 2) ^f	91/91 100% [96, 100]
GTa/b ^b	LDV/SOF	12 weeks	ION-2	83/87 95.4% [88.6, 98.7]
		24 weeks	ION-2	86/87

Population	Regimen	Duration	Evidence	SVR rate n/N % [95% CI] ^c
				98.9% [93.8, 100]
Treatment experienced, cirrhotic				
GT1a	Viekira PAK-RBV	12 weeks	Turquoise II (Arm A ^a)	25/26 96.2% [80.4, 99.9]
GT1b		12 weeks	Turquoise II (Arm A ^a)	45/46 97.8% [88.5, 99.9]
GT1a/b ^b	LDV/SOF	12 weeks	ION-2	19/22 86.4% [65.1, 97.1]
		24 weeks	ION-2	22/22 100% [84.6, 100]
Treatment experienced, cirrhotic, null responders				
GT1a (null responders)	Viekira PAK-RBV	24 weeks	Turquoise II (Arm B ^a)	39/42 92.9% [80.5, 98.5]

^aThe SVR rate is generated from a subgroup of a trial arm.

^bSVR results for ION studies cannot be separated by genotype, and treatment experience and cirrhotic status, therefore, results have been presented by treatment experience and cirrhotic status only. A breakdown by genotype is possible for ION-3 (as this trial only enrolled treatment naïve, non-cirrhotic patients) and is available in Table B-79, p325 of the submission.

^cSVR rates for the Viekira PAK / Viekira PAK-RBV studies were recalculated during the evaluation from the provided study CSRs. Exact confidence intervals were calculated using the confidence intervals for proportions command in Stata® 13.1.

^dThe proportion of patients achieving SVR for Pearl III are presented in the submission as 209/209, however the provided CSR reports 207/209 with 2 missing SVRs.

^eThe proportion of patients achieving SVR for Sapphire I are presented in the submission as 308/322, however the provided CSR reports 307/322.

^f95 patients were initially randomised to the Viekira PAK arm in Pearl II (Arm 2), however, four were excluded from the efficacy analysis as they were randomised prior to a substantial protocol amendment which resulted in the use of paritaprevir/ritonavir/ombitasvir fixed dose combination and an adjustment of the dose for dasabuvir. The safety analysis included all randomised patients.

Sources: Table 18, p174 of the Turquoise II CSR; Table 15, p136 of the Malachite I CSR; Table 14, p124 of the Malachite II CSR; Table 19, p187 of the Sapphire I CSR; Table 20, p198 of the Sapphire II CSR; Table 14, p172 of the Pearl II CSR; Table 15, p153 of the Pearl III CSR; Table 15, p149 of the Pearl IV CSR; Table B-79, p325 of the submission; Table B-80, p327 of the submission; Table B-83, p330 of the submission.

- 6.14 When there was more than one study providing data for a particular population, the results were pooled and have been presented below.

Table 6: Pooled sustained virologic response (SVR12) for genotype, cirrhotic status and treatment experience for Viekira PAK / Viekira PAK-RBV and LDV/SOF

Cirrhosis	Genotype	Viekira PAK±RBV SVR ^d n/N (k arms) % [95% CI]	Viekira PAK±RBV SVR pooled for GT1 ^{bd} n/N (k arms) % [95% CI]	LDV/SOF SVR ^d n/N (k arms) % [95% CI]
Treatment Naïve				
Non-cirrhotic	GT1a	471/491 (3) 96.1% [94.1, 97.7]	761/783 97.9% [94.8, 99.8] (63% GT1a)	768/792 (4) 98% [94, 99.9]
	GT1b	290/292 (2) 99.4% [95.1, 100]		
Cirrhotic	GT1a	59/64 (1) 92.2% [82.7, 97.4]	81/86 (1) 94.2% [87.1, 97.5] (74% GT1a)	63/65 (2) 96.9% [90.6, 100]
	GT1b	22/22 (1) 100% [84.6, 100]		
Treatment Experienced				
Non-cirrhotic	GT1a	185/192 (2) 97.3% [94.1, 99.5]	276/283 99.2% [94.9, 100] (68% GT1a)	169/174 (2) 97.4% [93.1, 99.8]
	GT1b	91/91 (1) 100% [96, 100]		
Cirrhotic	GT1a	25/26 (1) 96.2% [80.4, 99.9]	109/114 (2) 95.8% [90.6, 99.2] (60% GT1a)	41/44 (2) 95.6% [74.5, 100] ^c
	GT1b	45/46 (1) 97.8% [88.5, 99.9]		
	GT1a – non-responders	39/42 (1) 92.9% [80.5, 98.5]		

GT1a = genotype 1a; GT1b = genotype 1b; SVR = sustained virologic response; LDV/SOF = ledipasvir/sofosbuvir, CI = confidence interval; NA = not applicable.

^aThe SVR rate for ION-2 null responders is generated by pooling the 12 weeks and 24 weeks LDV/SOF arms for null responders (supplementary appendix to Afdhal et al 2014³³). These arms contain non-cirrhotic and cirrhotic patients, and patients of both genotypes, and therefore likely overestimates the SVR rate in GT1a, cirrhotic patients who were non-responders to prior treatment.

^bThe SVR rates are unable to be extracted from ION-1 and ION-2 by cirrhotic status and genotype. To make a comparison of Viekira PAK / Viekira PAK-RBV with LDV/SOF, the results for genotype 1a and genotype 1b in the Viekira PAK / Viekira PAK-RBV studies have been pooled. The proportion of patients with genotype 1a in the relevant arms of the LDV/SOF studies are: ION-1, 68.4%; ION-2, 78.4%; ION-3, 79.7%.

^cThe estimate for treatment experienced, cirrhotic patients from ION-2 contains some patients who are non-responders, and may be expected to have a lower response rate to LDV/SOF. These patients have been excluded from Arm A of Turquoise II.

^dSVR rates for the Viekira PAK / Viekira PAK-RBV studies and the ION studies were recalculated during the evaluation from the provided study CSRs and publications. When only a group contained data from only one source (one arm), exact confidence intervals were calculated using the confidence intervals for proportions command in Stata® 13.1. When multiple arms were used to generate a pooled estimate, this was performed using a random effects meta-analysis of proportions, with exact confidence intervals and adjusted using the Freeman-Tukey transformation in Stata® 13.1.

Source: generated during the evaluation from Table 18, p174 of the Turquoise II CSR; Table 15, p136 of the Malachite I CSR; Table 14, p124 of the Malachite II CSR; Table 19, p187 of the Sapphire I CSR; Table 20, p198 of the Sapphire II CSR; Table 14, p172 of the Pearl II CSR; Table 15, p153 of the Pearl III CSR; Table 15, p149 of the Pearl IV CSR; Table B-79, p325 of the submission; Table B-80, p327 of the submission; Table B-83, p330 of the submission.

- 6.15 SVR rates for Viekira PAK / Viekira PAK-RBV are high and exceed 95% in all groups relevant to the proposed listing with the following two exceptions:
- Treatment naïve, genotype 1a, cirrhotic patients – a subgroup of Arm A in Turquoise II, SVR rate is 92.2%.
 - Treatment experienced, non-responders, genotype 1a, cirrhotic patients – a subgroup of Arm B in Turquoise II, SVR rate is 92.9%.
- 6.16 The SVR rates for Viekira PAK / Viekira PAK-RBV were similar to those observed for LDV/SOF for similar patient groups, although bias and confounding cannot be ruled out due to the nature of the unadjusted indirect comparison. Therefore the magnitude of any relative treatment effect differences of Viekira PAK / Viekira PAK-RBV versus LDV/SOF cannot be established.
- 6.17 The ESC noted that GT1a-specific SVR estimates are not available for LDV/SOF and might be lower than the pooled GT1a>1b SVR rates reported.

Comparative harms

- 6.18 The safety data of Viekira PAK-RBV from the placebo-controlled trials of Sapphire I and Sapphire II are summarised below. Adverse events (AEs) were common in the placebo arm of the studies (73% – 82%) and slightly more common in the Viekira PAK-RBV arms (88% – 91%). However, serious adverse events were uncommon and occurred in 16 of 770 patients who received Viekira PAK-RBV, with 55 patients needing to be treated with Viekira PAK-RBV to experience one additional serious adverse event. Discontinuations among patients treated with Viekira PAK-RBV were uncommon and occurred in 7 of 770 patients (<1%).

Table 7: Summary of key safety results from Sapphire I and Sapphire II.

	Sapphire I		Sapphire II	
	Viekira PAK-RBV N=473	Placebo N=158	Viekira PAK-RBV N=297	Placebo N=97
	n (%)	n (%)	n (%)	n (%)
Median treatment duration	84 days	84 days	84 days	85 days
Proportion of patients receiving at least 75 days of treatment	464 (98.1)	157 (99.4)	293 (98.7)	95 (97.9)
Any AE	414 (87.5)	116 (73.4)	271 (91.2)	80 (82.5)
Any Severe AE	20 (4.2)	1 (0.6)	7 (2.4)	0
Any SAE	10 (2.1)	0	6 (2.0)	1 (1.0)
AE leading to discontinuation of study treatment	3 (0.6)	1 (0.6)	3 (1.0)	0
AE leading to interruption of study drug	4 (0.8)	0	3 (1.0)	0

AE leading to RBV dose modifications	26 (5.5)	0	19 (6.4)	1 (1.0)
Death ^a	1 (0.2)	0	0	0

AE = adverse event; SAE = serious adverse event; RBV = ribavirin.

^a Including non-treatment emergent adverse events.

Source: Table B-59, p267 of the submission, Table 32, p222 of the Sapphire I CSR and Table 32, p230 of the Sapphire II CSR.

- 6.19 The respective safety data of Viekira PAK and Viekira PAK-RBV and their comparison with LDV/SOF are summarised below. Treatment discontinuations were uncommon across all of the trials. Serious adverse events rates were similar for patients receiving Viekira PAK / Viekira PAK-RBV or LDV/SOF.

Table 8: Summary of key adverse events for Viekira PAK, Viekira PAK-RBV and LDV/SOF

	Malachite I, Malachite II, Pearl II, Pearl III, Pearl IV, Sapphire I, Sapphire II, Turquoise II			ION-1, ION-2, ION-3
	Viekira PAK N=592	Viekira PAK-RBV N=1805	Viekira PAK +/- RBV N=2397	LDV/SOF N=1080
	n (%)	n (%)	n (%)	n (%)
Any AE	424 (71.6)	1542 (85.4)	1966 (82)	806 (74.6)
Any SAE	7 (1.2)	48 (2.7)	55 (2.3)	34 (3.1)
AE to leading to discontinuation of study treatment	2 (0.3)	17 (0.9)	19 (0.8)	6 (0.6)
Deaths	0 (0)	5 (0.3)	5 (0.2)	0 (0)

AE = adverse event; SAE = serious adverse event; RBV = ribavirin; LDV/SOF = ledipasvir/sofosbuvir.

Source: Table B-34, p208; Table B-36, p216; Table B-60, p273; Table B-85, p333; Table B-87, p336; Table B-89, p338 of the submission.

Benefits/harms

- 6.20 A summary of the comparative benefits and harms for Viekira PAK / Viekira PAK-RBV versus 'no treatment' is presented in below, based on the evidence provided in the submission.

Table 9: The benefit/harm of Viekira PAK / Viekira PAK-RBV compared with no treatment

Patient group	Comparison	Benefits/harms**
Treatment-naïve		
Non-cirrhotic	GT1a	for every 100 patients treated with Viekira PAK-RBV for 12 weeks in comparison to receiving <u>no treatment</u> <ul style="list-style-type: none"> • Approximately 96 additional patients would be expected to achieve an SVR; and • Approximately 2 additional patients would experience a serious adverse event.
	GT1b	for every 100 patients treated with Viekira PAK for 12 weeks in comparison to receiving <u>no treatment</u> <ul style="list-style-type: none"> • Approximately 99 additional patients would be expected to achieve an SVR; and • Approximately 1 additional patient would experience a serious adverse event.

Patient group		Comparison	Benefits/harms**
Cirrhotic	GT1a	for every 100 patients treated with Viekira PAK-RBV for 12 weeks in comparison to receiving <u>no treatment</u>	<ul style="list-style-type: none"> • Approximately 93 additional patients would be expected to achieve SVR; and • Approximately 2 additional patients would experience a serious adverse event.
	GT1b	for every 100 patients treated with Viekira PAK-RBV for 12 weeks in comparison to receiving <u>no treatment</u>	<ul style="list-style-type: none"> • Approximately 100 additional patients would be expected to achieve SVR; and • Approximately 2 additional patients would experience a serious adverse event.
Treatment-experienced			
Non-cirrhotic	GT1a	for every 100 patients treated with Viekira PAK-RBV for 12 weeks in comparison to receiving <u>no treatment</u>	<ul style="list-style-type: none"> • Approximately 95 additional patients would be expected to achieve an SVR, and • Approximately 2 additional patients would experience a serious adverse event.
	GT1b	for every 100 patients treated with Viekira PAK for 12 weeks in comparison to receiving <u>no treatment</u>	<ul style="list-style-type: none"> • Approximately 100 additional patients would be expected to achieve an SVR, and • Approximately 1 additional patient would experience a serious adverse event.
Cirrhotic	GT1a*	for every 100 patients treated with Viekira PAK-RBV for 12 weeks in comparison to receiving <u>no treatment</u>	<ul style="list-style-type: none"> • Approximately 96 additional patients would be expected to achieve an SVR, and • Approximately 2 additional patients would experience a serious adverse event
	GT1b	for every 100 patients treated with Viekira PAK-RBV for 12 weeks in comparison to receiving <u>no treatment</u>	<ul style="list-style-type: none"> • Approximately 98 additional patients would be expected to achieve an SVR, and • Approximately 2 additional patients would experience a serious adverse event.
	GT1a prior null responders	for every 100 patients treated with Viekira PAK-RBV for 24 weeks in comparison to receiving <u>no treatment</u>	<ul style="list-style-type: none"> • Approximately 93 additional patients would be expected to achieve an SVR, and • Approximately 2 additional patients would experience a serious adverse event.

*except those who are null responders to prior treatments.

** Harm of Viekira PAK / Viekira PAK-RBV was based on pooled data of placebo-controlled trials of Sapphire I and Sapphire II. Given that the adverse event rates were similar across the 12 weeks and 24 weeks of Viekira PAK-RBV arms in Turquoise II randomised patients, safety data for 24 weeks treatment with Viekira PAK-RBV among the GT1a patients who are prior null responders were assumed to be the same as that of 12 weeks treatment with Viekira PAK-RBV and also sourced from pooled data of Sapphire I and Sapphire II. There were no placebo-controlled trials of Viekira PAK without RBV. Safety data for Viekira PAK without RBV were based on data presented in Table 6 above, assuming that there was no serious adverse event.

GT = genotype; SVR = sustained virologic response.

Source: Compiled during the evaluation

Clinical claim

- 6.21 The submission described Viekira PAK / Viekira PAK-RBV as superior in terms of efficacy and inferior in terms of safety compared with no treatment.
- 6.22 The submission described Viekira PAK / Viekira PAK-RBV as equivalent in terms of efficacy and safety to LDV/SOF. The submission's claim appeared reasonable within similar populations, although the magnitude of differences in terms of SVR rates or rates of adverse events was uncertain due to reliance on the single arm trials. There are differences in the safety profile of the drugs as well as the potential for safety issues. Patients on concomitant medications that are contraindicated with Viekira PAK / Viekira PAK-RBV were excluded from the Viekira PAK / Viekira PAK-RBV trials, although were permitted to be treated in the LDV/SOF trials. Therefore, the population able to be treated with LDV/SOF might be broader.

- 6.23 The PBAC agreed with the ESC and considered that the clinical claims in the submission were reasonable.
- 6.24 The PBAC recalled that ledipasvir/ sofosbuvir was recommended for the treatment of Genotype 1 CHC patients and that daclatasvir in combination with sofosbuvir was recommended for the treatment of Genotype 1 CHC in treatment naïve non-cirrhotic patients. The PBAC considered the evidence provided in the submission available in the public domain support the claim that Viekira PAK / Viekira PAK-RBV equivalent in terms of efficacy and safety to ledipasvir/ sofosbuvir in Genotype 1 naïve and experienced chronic hepatitis C (CHC) patients and daclatasvir in combination with sofosbuvir in in Genotype 1 treatment naïve non-cirrhotic patients.

Economic analysis

- 6.25 Given the rapidly changing treatment landscape for genotype 1 (GT1) CHC, the sponsor indicated that they were willing to accept a price on a cost-minimisation basis compared with LDV/SOF, should PBAC recommend LDV/SOF for PBS listing at the March 2015 meeting. As LDV/SOF was recommended at the March 2015 meeting, the ESC considered that a listing of Viekira PAK / Viekira PAK-RBV on a cost-minimisation basis to other IFN-free treatments was supported by the available clinical evidence.
- 6.26 The submission presented a modelled cost-utility analysis of Viekira PAK / Viekira PAK-RBV relative to a mixed comparator of no treatment and protease inhibitor plus PR. The evaluation presented a cost-utility analysis of Viekira PAK / Viekira PAK-RBV versus no treatment, consistent with previous considerations by the PBAC.
- 6.27 The economic model was structured as a Markov state-transition model, with 13 health states that described the progression of disease over the life time. The model comprised of two distinct time periods: the short term model covering the first year following the initiation of treatment (with four-weekly cycles) and the long-term model covering the remaining 29 years (with yearly cycles).

Table 10: Summary of model structure and rationale

Time horizon	30 years. <i>This is consistent with PBAC Advice.</i>
Outcomes	Quality-adjusted life years (QALYs) and Life years (LYs)
Methods used to generate results	Cohort expected-value analysis.
Cycle length	4 weekly cycles in first year, followed by yearly cycles. <i>This is appropriate.</i>
Transition probabilities	Based on a literature review. See Section C.2.1, and D.4 of the Commentary.
Discount rate	5% for costs and outcomes
Software package	Excel 2010

Source: compiled during the evaluation

- 6.28 The base-case economic analysis presented in the submission used results from Malachite I and Malachite II to estimate the SVR rates for non-cirrhotic patients, and used Turquoise II to estimate the SVR rates for cirrhotic patients. The submission justified this on the basis that the Malachite studies were the only ones that included a direct head-to-head comparison of Viekira PAK / Viekira PAK-RBV with a protease

inhibitor (telaprevir). As protease inhibitors are no longer the main comparator, the Commentary used pooled results of SVR rate for each patient subgroup (in terms of previous treatment history and cirrhotic status) from all appropriate Viekira PAK / Viekira PAK-RBV arms in all Viekira PAK / Viekira PAK-RBV studies, and presented the results of economic evaluation for each subpopulation relative to no treatment.

6.29 Key drivers of the model are summarised in Table 11 below.

Table 11: Key drivers of the model

Description	Method/Value	Impact
Transition probabilities between early states of HCV infections	Mild to F2: 0.049 F2 to F3: 0.113 F3 to F4: 0.115 <i>The ESC considered that these transition probabilities were higher than those previously accepted by the PBAC and were likely to overestimate the rapidity of the natural progression of the disease in CHC.</i>	High, favours Viekira PAK / Viekira PAK-RBV
Costs of some health states	CC: \$ [REDACTED] DCC: \$ [REDACTED] HCC: \$ [REDACTED] <i>The ESC considered the above costs were likely to be overestimated given that resource use was sourced from patients who are unlikely to represent average patients with these conditions</i>	High, favours Viekira PAK / Viekira PAK-RBV

CC = compensated cirrhosis; DCC = decompensated cirrhosis; HCC = hepatocellular carcinoma.
Source: compiled during the evaluation

6.30 Transition probabilities relating to the early stages of the disease, particularly from Mild CHC (F0/F1) to F2, F2 to F3 and F3 to F4, appeared to accelerate the natural history of the disease when compared to those used in other economic evaluations. The meta-analysis from which they were derived was based on a number of older longitudinal studies (some dating back to 1970), which, given the improvements in accuracy of available diagnostic methods and available treatments, may overestimate the progression of the disease (Telaprevir Public Summary Document (PSD), March 2012 PBAC meeting). The use of these values favoured Viekira PAK / Viekira PAK-RBV, and the model was particularly sensitive to this variable. Sensitivity analyses adjusting the transition probabilities to those used in a recent National Institute for Health and Care Excellence (NICE) evaluation were performed during the evaluation (which required the F2 and F3 health states to be combined into a 'moderate' health state), and the results indicated that the ICER increases substantially from \$15,000/QALY - \$45,000/QALY to \$15,000/QALY - \$45,000/QALY for treatment-naïve non-cirrhotic patients.

- 6.31 Health state costs used in the submission were sourced from a study commissioned by the Sponsor (referred to as the AbbVie MRU Audit in the submission). The Audit was a non-interventional, retrospective, observational study of patients with genotype 1 CHC conducted at two accredited liver clinics, and one liver transplant clinic. More details of the methods and results of this study are provided in an appendix to this ESC advice. Some health costs associated with liver disease in the submission are higher than in recent Australian publications:
- Compensated Cirrhosis (CC) (F4) (\$██████): The cost for CC was estimated from patients attending two liver treatment clinics for the first time and followed them up in a two-year period. A number of patients attending for the first time with CC developed complications associated with decompensated cirrhosis during the follow-up period (see Section C.4.1 of the Commentary). The majority of this health state cost (\$██████; ███%) is attributable to hospitalisations that are likely to relate to patients who have progressed to decompensated cirrhosis (e.g. for pleural effusion and cirrhosis / alcoholic hepatitis). This estimate is substantially higher than that used in other recent Australian studies (\$715 - \$909), which did not include costs relating to hospitalisation.
 - Decompensated cirrhosis (DCC) (\$██████): The cost for DCC was estimated from patients attending a liver transplant clinic. Resource use for patients attending a liver transplant clinic in the time leading up to a liver transplant is unlikely to represent the average cost of a patient with DCC, and likely to represent patients with more severe complications of DCC. Patients with DCC may be managed at a liver clinic, with only those at the severe end of the spectrum, and those suitable for transplantation being referred to a liver transplant clinic. This estimate is considerably higher than those provided in other recent Australian papers (\$11 748 - \$13,363), and may be attributable to the increased morbidity of the sample population.
 - Hepatocellular carcinoma (HCC) (\$██████): As with the estimates for DCC, it is possible that the patient population managed in a liver-transplant clinic prior to receiving a transplant may have a different resource use than the average patient with HCC in the Australian population (which may be managed by a liver clinic or oncologist). It is possible that this is an over-estimate of the health state cost for HCC, as it may also include some additional resources in preparation for the liver transplant. This estimate is substantially higher than the estimated cost for this health state from recent Australian studies (\$9,712 - \$17,872).
- 6.32 The ESC considered that MRU audit may not represent the average health costs and resource use for treating Australian patients with all stages of the disease across different clinical settings. Overall, the ESC considered that the health costs were overestimated.
- 6.33 The results of the economic evaluation (with no treatment as the comparator) are summarised below. The results suggested that Viekira PAK / Viekira PAK-RBV ██████████ in cirrhotic patients (except those who were prior null responders and received 24 weeks treatment). This outcome was primarily driven by an overall reduction in resource use in the Viekira PAK / Viekira PAK-RBV arm because fewer patients would be progressing (due to accelerated transition probabilities) to the later high cost health states (CC, DCC and HCC).

Table 12: Results of the economic evaluation of Viekira PAK/Viekira PAK-RBV relative to no treatment, by sub-genotype, treatment history and cirrhotic status

Treatment setting	Genotype	Regimen	Incremental Costs	Incremental QALYs	ICER
Non-cirrhotic					
Naïve	1a & 1b	Viekira PAK+/-RBV 12 weeks	\$ [REDACTED]	1.21	\$ [REDACTED]
Experienced	1a & 1b	Viekira PAK+/-RBV 12 weeks	\$ [REDACTED]	1.39	\$ [REDACTED]
Cirrhotic					
Naïve	1a & 1b	Viekira PAK-RBV 12 weeks	\$ [REDACTED]	2.51	[REDACTED]
Treatment experienced excl. GT1a prior null responders	1a & 1b	Viekira PAK-RBV 12 weeks	\$ [REDACTED]	2.50	[REDACTED]
Prior null responders	1a	Viekira PAK-RBV 24 weeks	\$ [REDACTED]	2.42	\$ [REDACTED]

QALY = quality-adjusted life-years; ICER = incremental cost-effectiveness ratio; GT = genotype.
Source: Compiled during evaluation.

6.34 Results of key sensitivity analyses, performed during the evaluation, for treatment-naïve patients (both cirrhotic and non-cirrhotic) are summarised below.

Table 13: Results of the univariate and multivariate sensitivity analyses, of the economic evaluation of Viekira PAK/Viekira PAK-RBV relative to no treatment, for treatment-naïve patients

Analysis	Variables changed in the model	ICER (Cost/QALY) Non-Cirrhotic	ICER (Cost/QALY) Cirrhotic
Base case		\$ [REDACTED]	[REDACTED]
#1 Using NICE transition probabilities for mild to moderate fibrosis and moderate fibrosis to cirrhosis*	Used in base case: Mild to F2: 0.049 F2 to F3: 0.113 F3 to F4: 0.115 Used in SA: Mild to Moderate: 0.025 Moderate to Cirrhosis (F4): 0.037	\$ [REDACTED]	[REDACTED]
#2 Using costs for CC, DCC and HCC health states from Visconti 2013	Used in base case: CC: \$ [REDACTED] DCC: \$ [REDACTED] HCC: \$ [REDACTED] Used in SA: CC: \$ [REDACTED] DCC: \$ [REDACTED] HCC: \$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
#3 Using costs from Visconti et al 2013	Various, presented in Table C.4.3 of the Commentary	\$ [REDACTED]	\$ [REDACTED]
#4 Using costs from Kirby 2014	Various, presented in Table C.4.3 of the Commentary	\$ [REDACTED]	\$ [REDACTED]
#5 Using the mean utility values from submission's literature review (and increment associated with SVR of [REDACTED] in the submission)	Various, presented in Table D.4.7 of the Commentary	\$ [REDACTED]	[REDACTED]
#6 Using utility values from Wright (2006) (used in NICE) and an increment associated with SVR of	Various, presented in Table D.4.7 of the Commentary	\$ [REDACTED]	[REDACTED]

Analysis	Variables changed in the model	ICER (Cost/QALY) Non-Cirrhrotic	ICER (Cost/QALY) Cirrhrotic
0.041			
Multivariate analysis (#1 & #2)	See above	\$ [REDACTED]	\$ [REDACTED]
Multivariate analysis (#1 & #2 & #5)	See above.	\$ [REDACTED]	\$ [REDACTED]

*When combining the F2 and F3 health states, transitions from F3 (with and without SVR) to HCC were removed.

SA = sensitivity analysis; NICE = National Institute for Health and Care Excellence; CC = compensated cirrhosis; DCC = decompensated cirrhosis; HCC = hepatocellular carcinoma; SVR = sustained virologic response.

Source: Compiled during the evaluation.

- 6.35 The above sensitivity analyses indicated that the model was most sensitive to transition probabilities between the early stages of CHC and the costs of the health states. When varying these variables simultaneously, the ICER increased from \$15,000/QALY - \$45,000/QALY to \$45,000/QALY - \$75,000/QALY for treatment-naïve non-cirrhrotic patients. Viekira PAK/Viekira PAK-RBV was no longer [REDACTED] for cirrhrotic patients.
- 6.36 The ESC noted that a large opportunity cost for all-oral interferon-free HCV regimens, including Viekira PAK/Viekira PAK-RBV, is expected. The listing of interferon-free HCV regimens would potentially reduce access to future cost-effective medicines. Given this, at the March 2015 PBAC meeting, the PBAC advised that new interferon-free regimens would be acceptably cost-effective at \$15,000/QALY, the lower end of the ICER range that PBAC has accepted for telaprevir or boceprevir (Ledipasvir/Sofosbuvir Public Summary Document– March 2015).
- 6.37 The relationship between the total regimen cost and the incremental cost per QALY gained is presented in figure below. To achieve an ICER of \$15,000/QALY, using sensitivity analyses #1 and #2 (the transition probabilities from mild to moderate fibrosis and moderate fibrosis to cirrhosis from NICE, and health state costs for compensated cirrhosis, decompensated cirrhosis and hepatocellular carcinoma from Visconti et al, 2013), the price of Viekira PAK / Viekira PAK-RBV for treatment-naïve non-cirrhrotic patients should be no more than \$ [REDACTED]. Using the submission’s base case a total regimen cost of approximately \$ [REDACTED] would achieve this same ICER (\$15,000/QALY).

Figure 1: Relationship between total regimen cost and the ICER for treatment-naïve non-cirrhrotic patients

[THIS FIGURE HAS BEEN REDACTED]

- 6.38 The pre-PBAC response disagreed with ESC’s view that the health cost for Hepatocellular carcinoma was overestimated but revised the following health state costs:
- \$ [REDACTED] for compensated cirrhosis F4 is compared to earlier proposed cost of \$ [REDACTED] attributable to hospitalisations likely to relate to patients who have progressed to decompensated cirrhosis.
 - \$ [REDACTED] for decompensated cirrhosis based on the assumption of a weighted proportion of patients attending a liver clinic or transplant clinic compared to earlier proposed cost of \$ [REDACTED].

- 6.39 The PBAC considered that the revised ICERS/QALY provided in the pre-PBAC was not informative as they were not presented against the appropriate comparator and the PBAC considered that health costs were overestimated and favoured Viekira PAK / Viekira PAK-RBV.
- 6.40 The PBAC also noted that ICER might be higher if the more conservative transition probabilities from the NICE assessment raised in the Commentary were applied to the model. In addition, the PBAC noted the other items, at the March 2015 meeting, modelling the cost-effectiveness of HCV treatment, using inputs and assumptions that the PBAC considered to be more appropriate for this disease.
- 6.41 Overall, the economic model presented in the submission favoured Viekira PAK / Viekira PAK-RBV and that applying more conservative inputs or scenarios increased the ICERS/QALY to a range higher than the PBAC considered cost-effective for the treatment of CHC.
- 6.42 Though all the data presented to the committee was based on unadjusted single arms of studies, the PBAC considered that it was reasonable to assume that one treatment course of Viekira PAK / Viekira PAK-RBV was as effective as one course of LDV/SOF for genotype 1 patients. The PBAC considered that there was no basis on which to recommend that Viekira PAK / Viekira PAK-RBV be more expensive than LDV/SOF for genotype 1 patients.
- 6.43 The PBAC reiterated that the most appropriate scenario to determine the cost of a treatment would be based on the largest groups of the total prevalent population, namely treatment naïve non-cirrhotic Genotype 1 patients as a proxy for all Genotype 1 patients. This cost of the entire treatment course should include the fees and mark ups associated with a General Schedule listing. The PBAC recommended that the cost to achieve a SVR12 should be independent of the treatment duration (such as 12 week or 24 weeks) considered to be appropriate to achieve a SVR in patients.
- 6.44 Though the PBAC did not accept all aspects of the economic model as submitted, at the comparative price setting of a treatment course, the Multivariate analysis (#1 & #2) presented in the sensitivity analyses above resulted in an ICER of \$15,000/QALY - \$45,000/QALY.

Drug cost/patient/course

- 6.45 \$ [REDACTED] / patient / course for all patients except for genotype 1a patients who are prior null responders (12 weeks).
- 6.46 \$ [REDACTED] / patient / course for genotype 1a prior null responders (24 weeks).
- 6.47 The submission indicated that the sponsor was willing to accept a price of Viekira PAK / Viekira PAK-RBV on a cost-minimisation basis in comparison with other interferon-free regimens, should they be listed.

Estimated PBS usage & financial implications

- 6.48 This submission was not considered by DUSC.
- 6.49 The submission has used an epidemiological approach to estimate the extent of use and financial implications upon the listing of interferon-free regimens. The submission assumed 100% market uptake with Viekira PAK / Viekira PAK-RBV as other interferon-free regimens were yet to be listed on the PBS.

Table 14: Estimated use and financial implications

	2016	2017	2018	2019	2020
Estimated extent of use					
Total number of patients managed in a liver treatment centre (not necessarily receiving treatment)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Patients treated with Viekira PAK ± RBV (GT 1)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Estimated Net cost to PBS/RPBS/MBS					
Net cost to PBS	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Net cost to MBS**	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Net cost to PBS/RPBS/MBS	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]

PI = protease inhibitor; PR = peginterferon and ribavirin

Source: compiled during the evaluation based on information contained in 'Section E model.xls'.

The redacted table above shows that the estimated use and financial implications of Viekira PAK / Viekira PAK-RBV to the health budget for the treatment of genotype 1 chronic hepatitis C (CHC) infection is less than 10,000 patients per year and more than \$100 million per year in each of the first five years of listing.

- 6.50 At its February 2015 meeting in consideration of LDV/SOF, SOF+PR and DCV+SOF, based on the treatment target set in the Fourth National Hepatitis C strategy 2014-2017 the DUSC estimated that the number of patients of all genotypes that would be treated over the first five years of listing of interferon-free treatment regimens, would be 6,600 in Year 1, 9,900 in Year 2 and 15,000 in Years 3-5. The number of genotype 1 patients treated with interferon-free regimens based on the DUSC

estimates was recalculated during the evaluation, assuming that 54.5% of treated patients had genotype 1 HCV infection and presented below^a.

Table 15: Number of Genotype 1 patients treated / year, estimated by DUSC.

	Year 1	Year 2	Year 3	Year 4	Year 5	Total
All genotypes	6600	9900	15000	15000	15000	61,500
Genotype 1*	3600	5400	8100	8100	8100	33,300

* For comparison. Assumes that 54.5% of the population being treated are genotype 1 (Bruggmann et al. (2014), rounded to the nearest 100 patients).

6.51 The estimated PBS usage and financial implications were uncertain. Key uncertainties included the estimation of the likely number of patients to be treated per year given:

- There is a large pool of people living with CHC infection (230,000); however there are constraints on the capacity of the health system to manage HCV;
- The likely number of patients treated in the submission following the listing of Viekira PAK / Viekira PAK-RBV is greater than the number of patients estimated by DUSC at the February 2015 meeting (see tables above, 10,000 – 50,000 vs 33,300 over the first five years of listing).
- The submission estimates that treatment capacity for all genotypes will increase by a factor of ■■■, immediately upon listing of IFN-free treatments. The ESC noted the sponsor disagreed in the PSCR with patient estimates from the DUSC February 2015 meeting and the treatment rates assumed in the Fourth National Hepatitis C strategy 2014-2017 and reiterated the estimates upon listing new oral DAA treatments would be higher as presented in the submission, which was based on the ALA advice (November 2014) of the current utilisation of PBS listed treatments and the upper limit of the that patient estimate of 15,000 recorded at the February 2014 Stakeholder meeting.
- The number of patients who have been deferring treatment to receive interferon-free therapy was unknown;
- Cost offsets for interferon-containing regimens are unlikely to increase over the first five years of listing as assumed by the submission, as patients are likely to be deferring treatment in anticipation of the availability of interferon-free regimens.

6.52 The PBAC recalled recent submissions and outcomes of stakeholder consultations since 2014 on the impact of all oral IFN-free CHC treatments on the capacity of the health system to treat CHC patients. The PBAC considered that the size of the likely treatment population remained uncertain. The PBAC noted that the submission estimated that the number of patients seeking treatment would be greater than those estimated by the DUSC. The PBAC noted the submission's claim that treatment capacity for all genotypes will increase by a factor of ■■■, immediately upon listing of IFN-free treatments was based on an estimate of the average hours spent by medical and nursing staff treating patients with interferon-containing regimens relative to a forecast of average hours with interferon-free regimens. The PBAC accepted that all oral treatments would result in less total hours spent by medical and

^a Consistent with the Recommendations from the Australian Liver Association on patients with a high clinical need for treatment with all oral regimes for chronic hepatitis C, November 2014

nursing staff treating patients but was concerned that it may not be appropriate to base the likely increase in population of patients being treated on this parameter alone as other factors are likely to impact on the number of treated patients. The time patients are treated across Australia may differ from those estimated in the submission, staff time saved with IFN-free treatments may be used for other tasks related or not related to CHC patients, that harder to treat patients may be prioritised, who require additional time of staff which is not only to prescribe and monitor medicines.

- 6.53 Though the magnitude of the primary care in the prescribing all oral treatment is unknown, the PBAC reiterated that it was reasonable to assume that the total number of patients estimated by DUSC over the next 5 years would remain appropriate in the context of a General Schedule listing, given that treatment would initially continue in specialist treatment centres; and that the uptake by general practitioners to become accredited to manage HCV may be low as noted in the NSW Hepatitis C Strategy 2014-2020.

Quality Use of Medicines

- 6.54 Viekira PAK-RBV may require up to 9 or 10 tablets per day which represents a substantial pill burden, particularly for patients already taking other medications. This compares unfavourably with LDV/SOF, which requires a single tablet per day.

Table 16: Daily tablet intake for patients receiving Viekira PAK / Viekira PAK-RBV

Population	Regimen	Tablets per day
G1b, non-cirrhotic	Viekira PAK	4
G1a and G1b cirrhotic <75kg	Viekira PAK-RBV 1000mg	9 ^a
G1a and G1b cirrhotic ≥75kg	Viekira PAK-RBV 1200mg	6 (10) ^b

^aPatients receiving a regimen containing ribavirin who weigh less than 75kg are required to take 5 ribavirin tablets per day (at 200mg each).

^bThe submission has also suggested that an alternative to 2 x 600mg ribavirin tablets for patients ≥ 75kg would be 6 x 200mg tablets, which would be permitted by the number of tablets available in the 200mg preparation (6 tablets x 28 days = 168).

Source: Compiled during the evaluation.

- 6.55 Patients who weigh less than 75kg will be prescribed the 168 x 200mg tablets of ribavirin that is co-packaged with Viekira PAK. At the end of 28 days, there will still be 28 tablets remaining. Patients should be made aware that there is a surplus of tablets. Of note is that the proposed Product Information of Viekira PAK / Viekira PAK-RBV offers 4 different preparations of Viekira PAK-RBV. This permits treatment with fewer ribavirin tablets and avoids issues with surplus tablets at the end of the 28 day period. The PSCR stated 'Ribavirin is co-packaged and will be supplied in the first instance in bottles of 168 X 200mg tablets or 56 X 600mg tablets'. The PSCR provided information of patient dosing cards and as part of the sponsor's Care patient support program, patients will receive individualised telephone calls.
- 6.56 The PBAC noted that the pre-PBAC response and the hearing that discussed that patient adherence with treatments requiring a different number of tablets per day would likely not be a major issue given the high treatment effectiveness and benefit of the all oral IFN-free treatments and the short treatment duration.

Financial Management – Risk Sharing Arrangements

- 6.57 The submission proposed a risk-sharing arrangement (RSA) to address some of the uncertainties surrounding the uptake rate of the new all-oral interferon-free treatment regimens. The proposed RSA is based on [REDACTED]. Acceptable rebates from the perspective of the sponsor and the Commonwealth will be negotiated [REDACTED].

Table 17: [REDACTED]

[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

- 6.58 The PBAC noted the proposed risk-sharing arrangement based on [REDACTED] but confirmed their view from the March 2015 meeting, and recommended that a RSA should consist of a cap on expenditure, with a 100% rebate for budget certainty. The Committee recommended that the Department negotiate RSAs based on DUSC estimates of the patient population and treatment course per patient for each medicine, in a manner that can be implemented and managed by the Department. The PBAC emphasised the importance of ensuring that these arrangements can be implemented in a way that would manage the overall cost to the Commonwealth for these medicines. Currently, the sponsors of Viekira PAK / Viekira PAK-RBV, SOF, LDV/SOF, and other sponsors of HCV treatments used in combination with SOF would be party to such arrangements.

For more detail on PBAC’s view, see section 7 “PBAC outcome”

7 PBAC Outcome

- 7.1 The PBAC recommended the Authority Required listing of paritaprevir/ritonavir/ombitasvir plus dasabuvir (Viekira PAK) and paritaprevir/ritonavir/ombitasvir plus dasabuvir with ribavirin (Viekira PAK-RBV) for the treatment of patients with genotype 1 chronic hepatitis C (CHC) infection on the basis of non-inferior efficacy and safety with Ledipasvir/Sofosbuvir (LDV/SOF), recommended in March 2015.
- 7.2 The PBAC recommended the price of a course of treatment for Viekira PAK / Viekira PAK-RBV should be the same as the price of a course of treatment with LDV/SOF for treatment naïve, non-cirrhotic genotype 1 patients.

- 7.3 The PBAC reiterated that the Committee recognised that new treatments of HCV resulted in high rates of sustained virological response, where the HCV virus could not be detected in the blood of patients 12 weeks after treatment commenced. The PBAC noted that the large number of comments and presentations from patients, health care professionals and organisations highlighted the benefits of the availability of new treatments, particularly IFN-free regimens.
- 7.4 The PBAC reiterated that it was appropriate that the new all oral treatment regimens be listed in the General Schedule, to facilitate the longer term objectives for access to treatment, increase treatment rates and outcomes with a view to treat all patients with CHC over time.
- 7.5 The submission proposed the current active treatments and no treatment as the comparator. The PBAC reiterated their previous view that the appropriate comparator was no treatment, in view of the broader context of infected individuals whose treatment preference is interferon-free therapies. However, following the recommendation to list sofosbuvir-containing regimens, the PBAC considered that these sofosbuvir-containing regimens were the most appropriate comparators for the consideration of all other oral HCV treatments
- 7.6 The PBAC noted the evidence used in submission was derived from head-to-head randomised controlled trials against telaprevir plus PR and placebo controlled randomised controlled trials, which supported the clinical claim that Viekira PAK / Viekira PAK-RBV was superior in terms of efficacy and inferior in terms of safety compared with no treatment. However, against the appropriate comparator, the evidence relied on unadjusted indirect comparison of single arms of individual studies with LDV/SOF. The PBAC considered that the comparative magnitude of the benefit (SVR12) of the treatment presented in the submission was uncertain due to the reliance on single arms of trials, some of which involved small number of patients. Overall, the PBAC considered that the clinical claim of Viekira PAK / Viekira PAK-RBV as equivalent in terms of efficacy and safety to LDV/SOF was supported.
- 7.7 The PBAC recalled that daclatasvir in combination with sofosbuvir was recommended for the treatment of Genotype 1 chronic hepatitis C (CHC) in treatment naïve non-cirrhotic patients. The PBAC considered the evidence provided in the submission available in the public domain support the claim that Viekira PAK / Viekira PAK-RBV equivalent in terms of efficacy and safety to daclatasvir in combination with sofosbuvir in this patient population.
- 7.8 The PBAC noted that
- among harder to treat cirrhotic treatment experienced patients, the point estimates were higher in Viekira PAK / Viekira PAK-RBV compared to 12 weeks treatment with LDV/SOF.
 - there are different contra-indications for treatment with Viekira PAK / Viekira PAK-RBV and LDV/SOF
 - the number of tablets per day required for treatment differed between Viekira PAK / Viekira PAK-RBV and LDV/SOF.

- 7.9 Overall, the PBAC considered that the impact of these differences on a patient achieving an SVR12 was unknown but the choice of treatment would be a clinician-patient decision.
- 7.10 The PBAC considered that there was no basis on which to make a cost effectiveness recommendation for Viekira PAK / Viekira PAK-RBV over ledipasvir/sofosbuvir.
- 7.11 The PBAC accepted the structure of the economic model presented in the submission and noted the ESC Advice on the parameters in economic model. Overall, the economic model presented in the submission favoured Viekira PAK / Viekira PAK-RBV and that applying more conservative inputs or scenarios increased the ICERs/QALY.
- 7.12 The PBAC recommended a risk-sharing arrangement between sponsors of all IFN-free oral treatments and the Department to give budget certainty to the Commonwealth, while not constraining prescribing and patient access to treatment.
- 7.13 In accordance with subsection 101(3BA) of the National Health Act 1953, the PBAC advised that the Committee is of the opinion that, on the basis of the material available at the July 2015 meeting, Viekira PAK / Viekira PAK-RBV should not be treated as interchangeable with other recommended treatments of CHC on an individual patient basis.
- 7.14 The PBAC noted that suitability of prescribing Viekira PAK / Viekira PAK-RBV by nurse practitioners would depend on the final listing conditions of Viekira PAK / Viekira PAK-RBV. The PBAC were of a mind that in principle nurse practitioners prescribing was likely to be suitable in the context of a shared care model.
- 7.15 The PBAC recommended that the Safety Net 20 Day Rule should apply to all the interferon-free DAA regimens, and would apply to this and previous recommendations for IFN-free treatments.
- 7.16 The submission is not eligible for an Independent Review, because the PBAC made a positive recommendation.
- 7.17 The PBAC acknowledged that there was a high clinical need for more effective and tolerable treatment for HCV. The PBAC noted that there is a large number (around 230,000) of patients with the chronic HCV who are untreated and that the utilisation of existing listings was low as patients were contraindicated or unwilling to take interferon. Based on the prevalence of HCV and the financial estimate presented in the submission, the PBAC considered that there would be a significant opportunity cost to the Commonwealth of listing oral treatments as their uptake would be substantially higher than currently subsidised medicines. The PBAC reiterated its view that the clinical management of individuals with HCV is moving so rapidly that a broader Government and community approach is needed to maximise the clinical outcomes and patient access to treatment. As well as subsidising new treatment on the PBS, other factors that increase the capacity to treat patients need to be explored.
- 7.18 The PBAC wished to re-advise the Minister that:
- While interferon-free oral direct acting antiviral (DAA) agents provide safe and

effective treatment options for patients with CHC, there is a substantial opportunity cost associated with the potential listing of these medicines. Given this large opportunity cost, the cost of a course of treatment should be set irrespective of the duration, and that other pricing policies be considered.

- The impact of the new antivirals on patients currently infected has been modelled by Sievert et al. (2014). This modelling shows that the number of people with chronic hepatitis C (CHC) will be reduced by 60% in 2030 compared to the base case of current treatment. The assumptions in the model include up to 13,500 people (including all fibrosis stages) are treated annually by 2018 and the DAA agents are expected to have rates of sustained virologic response (measured at 12 weeks, SVR12) up to 90% for genotype 1 and 80% for genotype 3 by 2016. The analyses accounted for mortality but did not consider re-infection.
- Advice from the Australian Liver Association (ALA) indicated that of the estimated 233,000 people living with Hepatitis C virus (HCV), 193,000 patients have been diagnosed. Listing of oral DAA agents may increase public and clinician awareness of the disease potentially leading to increased testing and diagnosis.
- The DUSC analysis shows that approximately 60 000 patients would be treated over 5 years, based on treatment targets in the Fourth National Hepatitis C Strategy 2014-2017, together with the advice from the ALA and February 2014 Stakeholder meeting (New oral antivirals for the Treatment of Hepatitis C). However, it is not clear how many people living with CHC will seek treatment, particularly if patients have to be seen in specialist liver clinics or wait for a referral to a liver clinic. Prescribing is likely to continue to be delivered through specialist clinics in the short-term until clinicians in other settings have learned how to use the DAA agents. Patients may still be required to go through the hospital system as part of their clinical management, which could be a limiting factor to uptake.
- Given the very large opportunity cost, one option would be to restrict access to treatment to those with the highest clinical need. The PBAC reiterated that it was inappropriate to restrict access, given the likely benefit of the DAA agents across the full spectrum of patients with CHC, from those with early disease to those patients with existing liver cirrhosis and severe portal hypertension, decompensated liver disease, or patients post liver transplant. The benefits in terms of avoidance or delay of decompensated cirrhosis, hepatocellular carcinoma and morbidity are likely to be seen earlier in the most severely ill, but population benefits, such as reduction in transmission of the disease, are likely to occur with wide access to treatment. This and other benefits may be also realised via other community-based programmes and strategies, such as those described in the Fourth National Hepatitis C Strategy 2014-2017.
- The high response (sustained virologic response measured at 12 weeks, SVR12) observed in the clinical trials may only be realised if the adherence of patients in Australia to treatment is similar to those in the clinical trials. While there is a patient preference for shorter treatments, and new shorter treatment regimens are currently being tested, for some patients, 24 weeks of treatment are necessary. Therefore it is critical that appropriate prescribing education be put in place to maximise the benefits to the Australian community.
- The treatment landscape of HCV treatment is changing rapidly, as new DAA agents or new combinations of DAA agents become available and treatment guidelines are regularly updated. It is likely that new DAA agents will be produced over the next 2 to 3 years that may further increase treatment options.

Outcome:

Recommended.

8 Recommended listing

- 8.1 Add new item:
Restriction to be finalised

9 Context for Decision

- 9.1 The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

10 Sponsor's Comment

AbbVie welcomes the PBAC's decision to recommend the reimbursement of Viekira PAK and Viekira PAK-RBV for patients with genotype 1 chronic hepatitis C and is committed to providing access for patients as quickly as possible.