Viekirax

Procedural steps taken and scientific information after the authorisation

Application number	Scope	Opinion/ Notification [1] issued on	Commission Decision Issued [2] / amended on	Product Information affected [3]	Summary
WS/2430	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing	16/03/2023	n/a		

[1] Notifications are issued for type I variations and Article 61(3) notifications (unless part of a group including a type II variation or extension application or a worksharing application). Opinions are issued for all other procedures.
[2] A Commission decision (CD) is issued for procedures that affect the terms of the marketing authorisation (e.g. summary of product characteristics, annex II, labelling, package leaflet). The CD is issued within two months of the opinion for variations falling under the scope of Article 23.1a(a) of Regulation (EU) No. 712/2012, or within one year for other procedures.
[3] SmPC (Summary of Product Characteristics), Annex II, Labelling, PL (Package Leaflet).

	authorisation, including the RMP - Other variation				
WS/2304/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Submission of the final reports from studies M14-423 (TOPAZ-1) and M14-222 (TOPAZ-II) listed as category 3 studies in the RMP for Viekirax and Exviera in order to fulfil MEA/018 for Viekirax and MEA/016 for Exviera. These are phase 3, open-label, multicentre, post-authorisation safety studies (PASS) to evaluate long-term outcomes with ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin (RBV) in adults with GT1 chronic HCV infection. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	01/09/2022	n/a		
N/0067	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	12/08/2022		PL	
WS/2216	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.	07/07/2022	n/a		

	Submission of the final report from study B20-146 listed as a category 3 study in the RMP. This is a non-imposed joint post-authorisation safety study to evaluate the risk of de novo hepatocellular carcinoma in patients with compensated cirrhosis treated with direct-acting antivirals for chronic hepatitis C (HCC De Novo PASS). C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				
SW/0065	Post Authorisation Safety Study results - EMEA/H/C/PSR/J/0038 – Variation	24/03/2022	30/05/2022	SmPC, Annex II and PL	The observational study and the systematic review/ meta-analysis did not show an increased risk of hepatocellular carcinoma recurrence in patients treated with direct-acting antivirals. The DAA-PASS study commitment is considered fulfilled and the respective products should be removed from the list of medicines under additional monitoring.
WS/2158	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	02/12/2021		Annex II	
IB/0062	B.III.1.a.2 - Submission of a new/updated or deletion of Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer	04/05/2021	n/a		

N/0061	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	24/02/2021	22/09/2021	PL	
WS/1972	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	26/11/2020	n/a		
IG/1291	C.I.11.a - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of wording agreed by the competent authority	23/09/2020	22/09/2021	Annex II	
PSUSA/10773 /202001	Periodic Safety Update EU Single assessment - dasabuvir, ombitasvir / paritaprevir / ritonavir	03/09/2020	n/a		PRAC Recommendation - maintenance
IA/0058	A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release)	26/08/2020	n/a		
II/0057	Update of section 4.5 of the SmPC in order to add information on drug-drug interaction with fostamatinib. The Package Leaflet is updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to	25/06/2020	09/10/2020	SmPC and PL	Co-administration of Viekirax with fostamatinib (Tavlesse), a novel substance indicated for the treatment of thrombocytopenia in adult patients with chronic immune thrombocytopenia, may result in increased risk of adverse events. The underlying mechanism for such drug-drug interaction is CYP3A4 inhibition by a potent inhibitor

	new quality, preclinical, clinical or pharmacovigilance data				ritonavir which is included in Viekirax. For more information, please refer to the Summary of Product Characteristics of Viekirax and Tavlesse.
WS/1663/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.13 To submit the final report from study P15-421, listed as a category 3 study in the RMP. This was a prospective, observational cohort study utilizing the Hepatitis C Therapeutic Registry and Research Network (HCV-TARGET) data to evaluate the clinical impact and real world frequency of Grade 3+ ALT elevations in patients being treated for Hepatitis C with paritaprevir with ritonavir (paritaprevir/r), ombitasvir and dasabuvir (3-DAA regimen) or paritaprevir/r and ombitasvir (2-DAA regimen) with or without ribavirin for Hepatitis C Infection (HCV) C.I.11.Z (Type IB): To change the final due date for the prospective safety study report in order to evaluate the recurrence of hepatocellular carcinoma associated with Viekirax and Exviera from Q2 2021 to Q2 2023. Annex II of the Product Information is updated accordingly. An updated RMP version 5.0 has also been submitted in order to convert the RMP to the new format and to remove some safety concerns and activities from the	03/10/2019	09/10/2020	Annex II	

	PhV Plan that have already been finalised. C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				
R/0054	Renewal of the marketing authorisation.	25/07/2019	19/09/2019	SmPC, Annex II, Labelling and PL	Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of Viekirax in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.
PSUSA/10367 /201901	Periodic Safety Update EU Single assessment - ombitasvir / paritaprevir / ritonavir	11/07/2019	n/a		PRAC Recommendation - maintenance
II/0053	Update of section 4.3 of the SmPC to contraindicate the concomitant use with lomitapide, a CYP3A4 substrate, and apalutamide, a strong CYP3A inducer, as well as update of section 4.5 of the SmPC on the potential interactions with apalutamide, encorafenib, ibrutinib and lomitapide. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to implement minor editorial changes. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	06/06/2019	08/07/2019	SmPC and PL	Update of Section 4.3 of the SmPC to contraindicate the concomitant use with lomitapide, a CYP3A4 substrate, and apalutamide, a strong CYP3A inducer, and of Section 4.5 of the SmPC to add information on the potential interactions with apalutamide, encorafenib, ibrutinib and lomitapide. The Package Leaflet is updated accordingly.

WS/1473	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of section 5.1 of the SmPC of Viekirax and Exviera in order to update the safety information based on study M14-004 listed as a category 3 study in the RMP. This is a multipart, open-label study to evaluate the safety and efficacy of ombitasvir/paritaprevir/ritonavir with or without dasabuvir coadministered with and without ribavirin in adults with Genotype 1 or 4 Chronic Hepatitis C Virus infection and Human Immunodeficiency Virus, Type 1 co-infection (TURQUOISE-I). In addition, the Marketing authorisation holder (MAH) took the opportunity to update section 5.1 of the SmPC of Exviera in alignment with section 5.1 of Viekirax SmPC. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	13/12/2018	08/07/2019	SmPC	The study M14-004 (TURQUOISE-I) was a Phase 2/3, multipart, open-label, multicenter study evaluating the safety and efficacy of ABT-450/r/ABT-267 with and without ABT-333 coadministered with and without ribavirin (RBV) for 12 or 24 weeks in adults with Hepatitis C Virus (HCV) GT1 or GT4/HIV-1 coinfection who were HCV treatment-naïve or HCV treatment-experienced with and without compensated cirrhosis. The efficacy results in this study are in line with what has been observed in patients without HIV coinfection and appear consistent along demographic and baseline HCV and HIV disease characteristics. No new safety issue has been identified and the safety profile is already well established. Section 5.1 of the SmPC has been updated to include information of the part 2 of TURQUOISE study.
WS/1472	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of section 5.1 of the SmPC of Viekirax and Exviera in order to update the efficacy and safety information based on study M12-999 listed as a category 3 study in the RMP. This is an open-label,	13/12/2018	08/07/2019	SmPC	The study (M12-999, CORAL-I) was designed to examine the safety and efficacy of treatment with ombitasvir/paritaprevir/ritonavir with dasabuvir (with or without ribavirin) in adult liver transplant recipients or renal transplant recipients. The primary objectives of this study were to assess safety and efficacy (the percentage of subjects achieving a 12-week sustained virologic response, SVR12 [HCV RNA <

	phase 2 study to evaluate the safety and efficacy of the combination of ombitasvir/paritaprevir/ritonavir with or without dasabuvir and with or without ribavirin (RBV) in adult liver or renal transplant recipients with Hepatitis C Virus (HCV) GT1 or GT4 infection (CORAL I). C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				lower limit of quantification {LLOQ} 12 weeks following treatment]) of ombitasvir/paritaprevir/ritonavir and dasabuvir and with or without ribavirin in HCV GT1-infected adult liver or renal transplant recipients and ombitasvir/paritaprevir/ritonavir with ribavirin in HCV GT4-infected adult liver transplant recipients. Overall, the SVR12 rates were fully in line what has been described for non-transplanted HCV patients. The adverse events presented are overall consistent with the known safety profile of ombitasvir/paritaprevir/ritonavir and dasabuvir when used with ribavirin. Section 5.1 of the SmPC has been updated to include information of the final study report of study CORAL I.
IG/1036	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	11/12/2018	08/07/2019	SmPC and PL	
PSUSA/10367 /201801	Periodic Safety Update EU Single assessment - ombitasvir / paritaprevir / ritonavir	20/09/2018	22/11/2018	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10367/201801.
II/0048	Submission of the final report from study M13-101 listed as a category 3 study in the RMP. This is an open-label study to examine the safety, antiviral activity and pharmacokinetics of Direct-Acting Antiviral Agent (paritaprevir/ritonavir/ombitasvir) treatment in combination with Peginterferon α-2a and Ribavirin (PegIFN/RBV) in Chronic Hepatitis C Virus (HCV) infected patients who had experienced virologic failure while participating in a previous MAH combination study.	18/10/2018	n/a		

	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				
WS/1348	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of sections 4.2, 4.3, 4.4 of the SmPC to reflect that Viekirax is contraindicated in patients with moderate hepatic impairment (Child-Pugh B) and update of section 5.2 to reflect that in HCV infected subjects paritaprevir AUC increased to 2.2- to 2.4 fold for those with compensated cirrhosis (Child-Pugh A) and 3- to 4-fold for those with Child-Pugh B cirrhosis based on the results of the final report from study (M14-227) listed as a category 3 study in the RMP. This is a Phase 3b study designed to evaluate the safety and efficacy of ombitasvir/paritaprevir/ritonavir and dasabuvir in HCV infected patients with Child-Pugh B decompensated cirrhosis. The package leaflet is updated accordingly. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	26/07/2018	31/08/2018	SmPC and PL	Pharmacokinetics of the combination of ombitasvir 25 mg, paritaprevir 200 mg, and ritonavir 100 mg, with dasabuvir 400 mg were evaluated in non-HCV infected subjects with mild (Child-Pugh A), moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment. In HCV infected subjects, in comparison to those without cirrhosis, paritaprevir AUC increased to 2.2- to 2.4-fold for those with compensated cirrhosis (Child-Pugh A) and 3- to 4-fold for those with Child-Pugh B cirrhosis. Viekirax is contraindicated in patients with moderate to severe hepatic impairment (Child-Pugh B or C).
II/0047	Submission of the final report from study (M14-567) listed as a category 3 study in the RMP. This is a randomized, open-label study to evaluate the safety	26/07/2018	n/a		Study M14-567, a Phase 2, randomized, open-label, multicenter study evaluated the safety and antiviral activity of coformulated ombitasvir/paritaprevit/ritonavir

	and efficacy of the co-administration of ombitasvir/ABT-450/Ritonavir (ombitasvir/ABT-450/r) with sofosbuvir (SOF) with or without ribavirin (RBV) in subjects with genotype 2 chronic hepatitis C virus (HCV) infection or genotype 3 HCV infection with or without Cirrhosis. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				(OBV/PTV/r) coadministered with sofosbuvir (SOF), with or without ribavirin (RBV) in treatment-naïve (TN) and treatment-experienced (TE) adults with GT2 HCV infection without cirrhosis and GT3 HCV infection with compensated cirrhosis or without cirrhosis. This study also assessed whether the addition of OBV/PTV/r could achieve comparable sustained virologic response (SVR) rates with shorter treatment durations of 6 and 8 weeks in subjects with GT2 HCV infection without cirrhosis. The results of this study support the safety and antiviral activity of 12 weeks of coformulated OBV/PTV/r coadministered with SOF with or without RBV in TN and TE adults with HCV GT3 infection with compensated cirrhosis or without cirrhosis. In addition, a high SVR 12 weeks post dosing (SVR12) rate was observed in subjects with GT2 infection who received OBV/PTV/r + SOF + RBV for 8 weeks. In contrast, shortening the treatment duration to 6 weeks resulted in a low SVR12 rate in subjects with HCV GT2 infection. A favorable safety profile was observed for all treatment regimens studied. No revisions to the Summary of Product Characteristics (SmPC) for Viekirax are recommended based on the results of this study.
WS/1400	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Submission of the final report from study M14-224: An Open-Label Study to Evaluate the Safety, Efficacy and Pharmacokinetics of Ombitasvir/ABT-450/Ritonavir (Ombitasvir/ABT-450/r) and Dasabuvir	19/07/2018	n/a		The study included a total of 29 subjects which received at least 1 dose of study drug (Part 1: N = 22; Part 2: N = 7). Efficacy was demonstrated in the majority of the subjects who had previously failed on either Direct-Acting Antiviral Agent (DAA) or Sofosbuvir (SOF)/ledipasvir treatment. Almost all subjects (28/29) were identified with a high viral load at study start which support that earlier treatment had failed. One subject in Part 1 experienced relapse by post-

	Co-administered With or Without Sofosbuvir (SOF) and Ribavirin (RBV) in Direct-Acting Antiviral Agent (DAA) Treatment- Experienced Adults With Genotype 1 Chronic Hepatitis C Virus (HCV) Infection, listed as a category 3 study in the RMP. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				treatment week 12. One subject in Part 2 was identified with on-treatment virologic failure. Sustained virologic response at week 12 (SVR12) was achieved in 21/22 (95.5%) of the subjects included in Part 1 and in 6/7 (85.7%) of the subjects included in Part 2. No subject who achieved SVR12 relapsed through the 48 weeks follow-up, which suggests that efficacy is comparable with previous clinical results associated with this treatment regimen No baseline or treatment-emergent substitutions were identified in NS5A or NS5B at signature amino acid positions except for the subject in Part 2 who experienced on-treatment virologic failure where treatment-emergent substitutions were observed in NS3 and NS5B at the time of failure. Except from that case, baseline polymorphism in NS3, NS5A or NS5B was not associated with impaired treatment results. Adverse events reported in this study were generally consistent with the established safety profile for ombitasvir/paritaprevir/ritonavir and dasabuvir, and for ribavirin (RBV) and the combination of these DAAs with RBV in previous studies of HCV subjects with and without cirrhosis. No subject experienced a treatment-emergent adverse events (TEAE) that met the criteria for severe cutaneous reactions or hepatic decompensation. One subject included in Part 1 discontinued the study drugs due to pneumonia and one subject in Part 2 experienced impaired glucose tolerance. No clinically relevant results of urinalysis, vital signs, or ECGs were observed. No deaths were reported. No new or different pattern compared with other clinical studies of these DAAs with or without RBV has been

					identified from this study. Based on the results of this study, the safety and efficacy profiles for Viekirax and Exviera remain unchanged and no changes to the product information are recommended.
T/0045	Transfer of Marketing Authorisation	30/05/2018	07/06/2018	SmPC, Labelling and PL	
WS/1342	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	12/04/2018	n/a		
IA/0043	A.6 - Administrative change - Change in ATC Code/ATC Vet Code	10/04/2018	07/06/2018	SmPC	
WS/1308/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of section 4.8 of the SmPC to add the adverse reaction anaphylactic reactions with unknown frequency following a safety review. The package leaflet is updated accordingly. C.I.3.b - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a procedure	22/03/2018	07/06/2018	SmPC and PL	

	concerning PSUR or PASS or the outcome of the assessment done under A 45/46 - Change(s) with new additional data submitted by the MAH C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
II/0039	Update of sections 4.3 and 4.5 of the SmPC to add disopyramide in the list of contraindicated medicines and in the list of medicines which interact with Viekirax. The Package Leaflet is updated accordingly. C.I.3.b - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a procedure concerning PSUR or PASS or the outcome of the assessment done under A 45/46 - Change(s) with new additional data submitted by the MAH	25/01/2018	05/03/2018	SmPC and PL	Ritonavir, one of the active substances contained in Viekirax, is a strong CYP3A inhibitor. Given that disopyramide is partly eliminated by metabolism via CYP3A4x, co-administration with ritonavir might result in increased disopyramide exposures. As disopyramide has a narrow therapeutic index, a risk for a clinically relevant interaction between disopyramide and CYP3A4 inhibitors cannot be excluded. Furthermore, literature articles report potentially life-threatening outcome of concomitant treatment of CYP3A4 inhibitors with disopyramide. Therefore, disopyramide has been contraindicated with Viekirax.
WS/1302	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Submission of the final report from study (M13-102) listed as a category 3 study in the RMP. This is a phase 3, long-term follow-up study to assess resistance and durability of response to direct-acting antiviral agent (DAA) therapy in subjects who participated in phase 2 or 3 clinical studies for the treatment of chronic hepatitis C virus (HCV) infection.	18/01/2018	n/a		Results from study M13-102 indicated a durable virologic response and a low frequency of events related to liver disease and/or HCV infection over an observation period of up to 3 years in subjects who achieved SVR12 in a previous applicant DAA study. Treatment emergent resistance-associated substitutions in NS3 declined over time, while most substitutions in NS5A persisted through PT Week 96. Due to the limited data, no conclusions can be made on the persistence of treatment-emergent substitutions in NS5B. Based on these results the CHMP did not warrant an update of the product information.

	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				
IB/0040/G	This was an application for a group of variations. B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.a.3.a - Change in batch size (including batch size ranges) of AS or intermediate - Up to 10-fold increase compared to the originally approved batch size	10/01/2018	n/a		
PSUSA/10367 /201701	Periodic Safety Update EU Single assessment - ombitasvir / paritaprevir / ritonavir	14/09/2017	15/11/2017	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10367/201701.
WS/1225/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Submission of the final reports for two phase IIIb studies (RUBY-I or M14-226 and RUBY-II or M15-461) listed as category 3 studies in the RMP. These are open-label studies evaluating the safety and efficacy of ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin in hepatitis C virus infected patients with several renal impairment or end-stage renal disease with or without	14/09/2017	15/11/2017	SmPC	Viekirax (ombitasvir / paritaprevir / ritonavir) and Exviera (dasabuvir) with or without ribavirin were assessed in 68 subjects with genotype 1 infection with or without cirrhosis who have severe renal impairment or end-stage renal disease (ESRD) in RUBY-I study. The overall safety profile in subjects with severe renal impairment was similar to that seen in prior Phase III studies in subjects without severe renal impairment, except that a greater proportion of subjects required intervention due to ribavirin-associated decreases in serum haemoglobin. The mean baseline haemoglobin level was 12.1 g/dL and the mean decline in haemoglobin at the end of treatment for subjects taking ribavirin was 1.2 g/dL. Thirty-nine of the 50 subjects who

	compensated cirrhosis. Consequently, the sections 4.8 and 5.1 of the SmPC are updated to reflect the main results of study M14-226 (RUBY-I). In addition, the MAH took the opportunity to make a correction in the product information of Viekirax. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				received ribavirin required interruption of ribavirin, and 11 of these subjects were also treated with erythropoietin. Four subjects experienced a haemoglobin level < 8 g/dL. Two subjects received a blood transfusion. Adverse events of anaemia were not seen in the 18 GT1b-infected subjects who did not receive ribavirin. Viekirax with or without dasabuvir was also evaluated without ribavirin in 18 GT1a- and GT4-infected patients; no adverse events of anaemia were seen in these subjects.
WS/1169	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	06/07/2017	n/a		
WS/1181/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Submission of the final report for two phase IIIb studies (studies M13-774 and M13-862) to support the 3 direct-acting antiviral regimen administered with and without ribavirin for 12 weeks for chronic hepatitis C virus genotype 1 infected, treatment-	22/06/2017	n/a		Final results of two Phase 3b studies (Studies M13-774, MALACHITE-I and M13-862, MALACHITE-II) were submitted to support the 3-direct-acting antivirals (DAA) regimen administered with and without ribavirin (RBV) for 12 weeks for chronic hepatitis C virus (HCV) genotype 1 (GT1)-infected, treatment-experienced and treatment-naïve subjects without cirrhosis. These studies showed that 3-DAA + RBV regimen in treatment naive and pegylated (PEG) treatment experienced GT1 infected patients without cirrhosis was highly effective achieving sustained virologic

	experienced and treatment-naïve subjects without cirrhosis, listed as category 3 studies in the RMP. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				response rates (SVR12) of >97%. A 12 Week 3-DAA regimen in GT1b infected patients was also highly effective (SVR12 97.6%) and had a superior safety profile. Based on the totality of the efficacy and safety data in Studies M13-774 and M13-862, no changes to the information in the Summary of Product Characteristics for Viekirax and Exviera are considered necessary.
WS/1079	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of sections 4.4 and 4.5 of the SmPC to include a warning on the concomitant use of sirolimus and everolimus with dasabuvir and ombitasvir/paritaprevir/ritonavir and to update the information on the drug-drug interaction with sirolimus and everolimus. The Package Leaflet is updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	23/03/2017	15/11/2017	SmPC and PL	Co-administration of dasabuvir and ombitasvir/paritaprevir/ritonavir with systemic tacrolimus, sirolimus or everolimus increases the concentrations of the immunosuppressant due to CYP3A inhibition by ritonavir (see section 4.5). Serious and/or life threatening events have been observed with co-administration of dasabuvir and ombitasvir/paritaprevir/ritonavir with systemic tacrolimus, and a similar risk can be expected with sirolimus and everolimus. Avoid concomitant use of tacrolimus or sirolimus with dasabuvir and ombitasvir/paritaprevir/ritonavir unless the benefits outweigh the risks. If tacrolimus or sirolimus are used together with dasabuvir and ombitasvir/paritaprevir/ritonavir, caution is advised, and recommended doses and monitoring strategies can be found in section 4.5. Everolimus cannot be used due to lack of suitable dose strengths for dose adjustments. Tacrolimus or sirolimus whole blood concentrations should be monitored upon initiation and throughout coadministration with dasabuvir and ombitasvir/paritaprevir/ritonavir and the dose and/or

					dosing frequency should be adjusted as needed. Patients should be monitored frequently for any changes in renal function or tacrolimus or sirolimus associated adverse events. Refer to the tacrolimus or sirolimus Summary of Product Characteristics for additional dosing and monitoring instructions.
WS/1063	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	23/03/2017	n/a		
WS/1106	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	16/03/2017	15/11/2017	SmPC	Co-administration of Exviera and ombitasvir/paritaprevir/ritonavir with systemic tacrolimus increases the concentrations of tacrolimus due to CYP3A inhibition by ritonavir (see section 4.5). Serious and/or life threatening events have been observed with co-administration of Exviera and ombitasvir/paritaprevir/ritonavir with systemic tacrolimus. Avoid concomitant use of tacrolimus with Exviera and ombitasvir/paritaprevir/ritonavir unless the benefits outweigh the risks. If tacrolimus with Exviera and ombitasvir/paritaprevir/ritonavir are used concomitantly, tacrolimus should not be administered on the day Exviera and ombitasvir/paritaprevir/ritonavir are initiated. Beginning the day after Exviera and ombitasvir/paritaprevir/ritonavir are initiated, reinitiate tacrolimus at a reduced dose based on tacrolimus whole blood concentrations. The recommended tacrolimus dose is

					0.5 mg every 7 days (see section 4.5). Tacrolimus whole blood concentrations should be monitored upon initiation and throughout co-administration with Exviera and ombitasvir/paritaprevir/ritonavir and the dose and/or dosing frequency should be adjusted as needed. Patients should be monitored frequently for any changes in renal function or tacrolimus-associated adverse events. Refer to the tacrolimus Summary of Product Characteristics for additional dosing and monitoring instructions.
WS/1114	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	23/02/2017	15/11/2017	SmPC and PL	Results from the GARNET study (M15-684) showed that treatment duration of 8 weeks with Exviera or Viekirax may be considered in previously untreated genotype 1b-infected patients with minimal to moderate fibrosis. When assessing severity of liver disease using non-invasive methods, a combination of blood biomarkers or the combination of liver stiffness measurement and a blood test improves accuracy and should be undertaken prior to 8 week treatment in all patients with moderate fibrosis.
A20/0018	Pursuant to Article 20 of Regulation (EC) No 726/2004, the European Commission requested the opinion of the European Medicines Agency further to a signal of hepatitis B reactivation in patients co-infected with HBV/HCV and concerns over the recurrence of hepatocellular carcinoma in patients using direct-acting antivirals in the context of interferon-free treatment of chronic hepatitis C. The PRAC was requested to assess the impact thereof on the benefit-risk balance of authorised direct-acting antivirals, namely Daklinza, Exviera, Harvoni, Olysio, Sovaldi and Viekirax and to give its opinion on	15/12/2016	23/02/2017	SmPC, Annex II and PL	Please refer to the assessment report: Direct-acting antivirals indicated for treatment of hepatitis C (interferon-free) - EMEA/H/A-20/1438

	whether the marketing authorisation of these products should be maintained, varied, suspended or revoked.				
PSUSA/10367 /201607	Periodic Safety Update EU Single assessment - ombitasvir / paritaprevir / ritonavir	09/02/2017	n/a		PRAC Recommendation - maintenance
II/0025	Update of sections 4.3 and 4.5 of the SmPC to add three additional contraindication medications, dronedarone, lurasidone and ranolazine. The Package Leaflet is updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	15/12/2016	26/01/2017	SmPC and PL	Ranolazine, dronedarone and lurasidone are primarily metabolised by the cytochrome P450 (CYP3A). This means that inhibitors and inducers of CYP3A have the potential to interact on these active substances. The exposure of these active substances could be increased which may lead to potential toxicities, including a dose-related QTc prolongation. Their co-administration with potent cytochrome P450 (CYP) 3A4 inhibitors (such as ritonavir) is also contraindicated. Therefore, given the potential safety concerns related to potential changes in exposures of ranolazine, dronedarone and lurasidone when co-administrated with the 2-DAA (Direct Acting Antivirals) or 3-DAA regimens, the CHMP considers that the product information of the medicinal product containing the association of ombitasvir / paritaprevir / ritonavir (Viekirax) should be updated to reflect that the co-administration with ranolazine, dronedarone and lurasidone is contraindicated.
IG/0744	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	18/11/2016	26/01/2017	SmPC, Labelling and PL	

WS/0919	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of sections 4.2 and 5.2 of the SmPC in order to reflect the findings of study M14-226 in patients with HCV infection and several renal impairment or End Stage Renal Disease. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	10/11/2016	26/01/2017	SmPC	
II/0022/G	This was an application for a group of variations. Update of section 4.2 of SmPC to recommend a decrease in treatment duration of 12 weeks in GT4 cirrhotic patients, with a consequential change to sections 4.4 and 5.1 and with minor editorial consequential change to section 5.2. In addition, the applicant took the opportunity to place the required safety features on the packaging (i.e. Unique Identifier – 2D Barcode and Human Readable Data). C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to	21/07/2016	18/08/2016	SmPC and Labelling	The results from the Phase III study M11-665 (randomised, open-label study to evaluate the safety and efficacy of ombitasvir/ABT-450/ritonavir co-administered with ribavirin in adults with genotype 4 chronic hepatitis C virus infection and cirrhosis) showed that a decrease in treatment duration of 12 weeks for patients with compensated cirrhosis and infected with genotype 4 is justified. The efficacy results observed showed a high response rate and none of the patients experienced a relapse despite the shortened treatment duration. There were no new safety signals in this study. Adverse events reported were in line with the known safety profile of Viekirax. Consequently section 4.2 of SmPC was updated to recommend a decrease in treatment duration of 12 weeks in genotype 4 cirrhotic patients, with a consequential change to sections 4.4 and 5.1 and with minor editorial consequential change to section 5.2.

	new quality, preclinical, clinical or pharmacovigilance data				
IB/0020	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	26/07/2016	n/a		
WS/0961/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Submission of the final study reports for the Phase 3 and Phase 2 studies included in the initial marketing authorisation applications and submission of the final study report of Phase 3b Study included in previous finalised type II variation. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission	14/07/2016	n/a		

	of studies to the competent authority C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				
IB/0024/G	This was an application for a group of variations. A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	11/07/2016	n/a		
PSUSA/10367 /201512	Periodic Safety Update EU Single assessment - ombitasvir / paritaprevir / ritonavir	07/07/2016	n/a		PRAC Recommendation - maintenance
IB/0023/G	This was an application for a group of variations. B.I.a.1.z - Change in the manufacturer of AS or of a	24/06/2016	n/a		

	starting material/reagent/intermediate for AS - Other variation B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation				

WS/0896/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of section 4.5 of the SmPC in order to update Drug-Drug interactions of Exviera and Viekirax with metformin, sulfamethoxazole/trimethoprim, cyclobenzaprine, carisoprodol, hydrocodone/ acetaminophen (paracetamol) or diazepam, dolutegravir, abacavir/lamivudine and sufosbuvir. The Package Leaflet is updated accordingly. In addition, the Worksharing applicant (WSA) took the opportunity to update the list of local representatives for Spain in the Package Leaflet for both products. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance	28/04/2016	18/08/2016	SmPC and PL	No dose adjustment is needed for diazepam, paracetamol, carisoprodol, cyclobenzaprine, metformin, sofosbuvir, abacavir/lamivudine and dolutegravir when co-administered with Exviera +/- Viekirax. A reduction of hydrocodone dose by 50% and/or clinical monitoring should be considered when administered with Exviera +/- Viekirax. No dose adjustment is needed for Exviera +/- Viekirax when co-administered with sulfamethoxazole + trimethoprim. For more information please refer to the Summary of Product Characteristics.

	data				
PSUSA/10367 /201507	Periodic Safety Update EU Single assessment - ombitasvir / paritaprevir / ritonavir	25/02/2016	28/04/2016	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10367/201507.
WS/0878/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of sections 4.2, 4.8 and 5.1 of the SmPC in order to update the safety information to recommend treatment of patients with GT1b HCV infection without cirrhosis or with compensated cirrhosis with only Viekirax and Exviera as result of analysis of study M14-490. In addition, section 4.4 and 4.6 are updated based on an EMA request during procedure MEA/H/C/WS/808 in order to bring the statement on contraceptive use with ribavirin into line with that for other ribavirin products. The Package Leaflet is updated accordingly. Furthermore the Worksharing applicant (WSA) is implementing the ATC code as indicated by the WHO acceptance in section 5.1 of the SmPC. The WSA took also the opportunity to update the contact details for the local representative for Estonia in the package leaflet. A.6 - Administrative change - Change in ATC Code/ATC Vet Code C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance	25/02/2016	28/04/2016	SmPC and PL	The efficacy profile of Viekirax and dasabuvir or Exviera and ombitasvir/paritaprevir/ritonavir without ribavirin yielded excellent efficacy in subjects without cirrhosis, and with compensated cirrhosis. The safety profile of Viekirax and dasabuvir or Exviera and ombitasvir/paritaprevir/ritonavir were similar in subjects without cirrhosis, and with compensated cirrhosis with the exception of increased rates of transient hyperbilirubinemia when ribavirin was part of the regimen. In subjects receiving Viekirax and dasabuvir or Exviera and ombitasvir/paritaprevir/ritonavir without ribavirin, adverse events typically associated to ribavirin were less frequent and no subjects permanently discontinued treatment due to adverse reactions. Extreme caution must be taken to avoid pregnancy in female patients and female partners of male patients when Viekirax/exviera is taken in combination with ribavirin; refer to the Summary of Product Characteristics for ribavirin for additional information.

	data C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation				
IB/0016	B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	10/02/2016	n/a		
IB/0014	B.II.f.1.b.1 - Stability of FP - Extension of the shelf life of the finished product - As packaged for sale (supported by real time data)	27/01/2016	28/04/2016	SmPC	
WS/0873	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of sections 4.2, 4.4, 4.8 and 5.2 of the SmPC in order to update the safety information related to use in patients with hepatic impairment based on post-marketing cases of hepatic decompensation and hepatic failure, including liver transplantation or fatal outcomes, reported in patients treated with Viekirax in combination with Exviera. The Package Leaflet is updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	17/12/2015	25/01/2016	SmPC and PL	
IG/0638	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging	08/12/2015	n/a		

	site				
IG/0617	C.I.8.a - Introduction of or changes to a summary of Pharmacovigilance system - Changes in QPPV (including contact details) and/or changes in the PSMF location	10/11/2015	n/a		
IA/0007	B.I.a.3.a - Change in batch size (including batch size ranges) of AS or intermediate - Up to 10-fold increase compared to the originally approved batch size	09/10/2015	n/a		
II/0004	Update of section 5.3 of the SmPC to reflect the results of recently completed carcinogenicity study. Furthermore, the MAH took the opportunity to update the details of Finnish local representative in the PL. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	24/09/2015	25/01/2016	SmPC	In this variation the MAH updated the PI to add information that one of Viekirax's components, ombitasvir, was not carcinogenic in a 2-year rat study.
IG/0591/G	This was an application for a group of variations. A.1 - Administrative change - Change in the name and/or address of the MAH C.I.8.a - Introduction of or changes to a summary of Pharmacovigilance system - Changes in QPPV (including contact details) and/or changes in the PSMF location	24/07/2015	25/01/2016	SmPC, Labelling and PL	

IB/0002/G	This was an application for a group of variations. B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.d.1.a.4 - Stability of AS - Change in the re-test period/storage period - Extension or introduction of a re-test period/storage period supported by real time data B.I.d.1.a.4 - Stability of AS - Change in the re-test period/storage period - Extension or introduction of a re-test period/storage period supported by real time data B.I.c.2.z - Change in the specification parameters and/or limits of the immediate packaging of the AS - Other variation	20/07/2015	n/a		
IG/0541/G	This was an application for a group of variations. B.II.e.2.b - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Addition of a new specification parameter to the specification with its corresponding test method B.II.e.2.c - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete	27/03/2015	n/a		

	parameter)				