EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Exviera

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).

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	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/0055	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/0053	Post Authorisation Safety Study results - EMEA/H/C/PSR/J/0038 – Variation	24/03/2022	02/06/2022	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	02/06/2022	Annex II	
N/0050	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	24/02/2021	16/09/2021	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	16/09/2021	Annex II	
PSUSA/10773 /202001	Periodic Safety Update EU Single assessment - dasabuvir, ombitasvir / paritaprevir / ritonavir	03/09/2020	n/a		PRAC Recommendation - maintenance
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	03/10/2019	30/09/2020	Annex II	

	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 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/0045	Renewal of the marketing authorisation.	25/07/2019	26/09/2019	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 Exviera in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.
PSUSA/10363 /201901	Periodic Safety Update EU Single assessment - dasabuvir	11/07/2019	n/a		PRAC Recommendation - maintenance

II/0044	Update of section 4.3 of the SmPC to contraindicate the concomitant use with apalutamide, a strong CYP3A inducer, as well as to update section 4.5 of the SmPC on the interaction with apalutamide. 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	01/07/2019	SmPC and PL	Update of Section 4.3 of the SmPC to contraindicate the concomitant use with apalutamide, a strong CYP3A inducer, and to add information in Section 4.5 of the SmPC on the interaction with apalutamide. 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.	13/12/2018	01/07/2019	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.

	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				
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, 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	13/12/2018	01/07/2019	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 < 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	01/07/2019	SmPC and PL	
PSUSA/10363 /201801	Periodic Safety Update EU Single assessment - dasabuvir	20/09/2018	12/11/2018	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for

					PSUSA/10363/201801.
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	04/10/2018	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).
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	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

	and Pharmacokinetics of Ombitasvir/ABT-450/Ritonavir (Ombitasvir/ABT-450/r) and Dasabuvir 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				load at study start which support that earlier treatment had failed. One subject in Part 1 experienced relapse by post-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/0038	Transfer of Marketing Authorisation	30/05/2018	31/05/2018	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/0036	A.6 - Administrative change - Change in ATC Code/ATC Vet Code	10/04/2018	31/05/2018	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.	22/03/2018	31/05/2018	SmPC and PL	

	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 C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
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. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	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.
PSUSA/10363 /201701	Periodic Safety Update EU Single assessment - dasabuvir	14/09/2017	10/11/2017	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10363/201701.
WS/1225/G	This was an application for a group of variations following a worksharing procedure according to	14/09/2017	10/11/2017	SmPC	Viekirax (ombitasvir / paritaprevir / ritonavir) and Exviera (dasabuvir) with or without ribavirin were assessed in 68

	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 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				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 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-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	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 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	23/03/2017	10/11/2017	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

	updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				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	16/03/2017	10/11/2017	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

	data				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	10/11/2017	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.
A20/0017	Pursuant to Article 20 of Regulation (EC) No	15/12/2016	23/02/2017	SmPC, Annex	Please refer to the assessment report:

	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 whether the marketing authorisation of these products should be maintained, varied, suspended or revoked.			II and PL	Direct-acting antivirals indicated for treatment of hepatitis C (interferon-free) - EMEA/H/A-20/1438
PSUSA/10363 /201607	Periodic Safety Update EU Single assessment - dasabuvir	09/02/2017	n/a		PRAC Recommendation - maintenance
IB/0026	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)	11/01/2017	10/11/2017	SmPC	
IG/0744	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	18/11/2016	23/02/2017	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.	10/11/2016	23/02/2017	SmPC	

	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				
IB/0019	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	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 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				
PSUSA/10363 /201512	Periodic Safety Update EU Single assessment - dasabuvir	07/07/2016	n/a		PRAC Recommendation - maintenance
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,	28/04/2016	23/02/2017	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 +

	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 data				trimethoprim. For more information please refer to the Summary of Product Characteristics.
PSUSA/10363 /201507	Periodic Safety Update EU Single assessment - dasabuvir	25/02/2016	21/04/2016	SmPC and PL	Please refer to Exviera-PSUSA/00010363/201507 EPAR: Scientific conclusions adn grounds recommending the variation to the terms of marketing authorisation.
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.	25/02/2016	21/04/2016	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.

	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 data C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation				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.
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	17/12/2015	25/01/2016	SmPC and PL	

	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				
IG/0638	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	08/12/2015	n/a		
IA/0011	A.7 - Administrative change - Deletion of manufacturing sites	03/12/2015	n/a		
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		
II/0006	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	24/09/2015	25/01/2016	SmPC	In this variation the MAH updated the PI to add information that Exviera was not carcinogenic in a 2-year rat study.

	new quality, preclinical, clinical or pharmacovigilance data				
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	
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 parameter)	27/03/2015	n/a		
IB/0003	B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation	09/03/2015	n/a		
IB/0002	B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement	27/02/2015	n/a		

	or addition) for the AS or a starting material/intermediate				
IAIN/0001/G	This was an application for a group of variations. B.I.a.1.a - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place 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	20/02/2015	n/a		