Harvoni

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/2356	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	12/01/2023	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				
IB/0108	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)	10/11/2022		SmPC and PL	Product information section 6.3 is updated to reflect the shelf-life extension of the finished product Harvoni 33.75 mg/150 mg coated granules (EU/1/14/958/004) and Harvoni 45 mg/200 mg coated granules (EU/1/14/958/005) as packaged for sale from 36 months to 48 months.
WS/2222	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 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	07/07/2022	n/a		
SW/0106	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.
PSUSA/10306	Periodic Safety Update EU Single assessment -	05/05/2022	n/a		PRAC Recommendation - maintenance

/202110	sofosbuvir / ledipasvir				
IA/0103	B.II.c.2.a - Change in test procedure for an excipient - Minor changes to an approved test procedure	10/12/2021	n/a		
WS/2157	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	30/09/2021	30/05/2022	Annex II	
IB/0100	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)	25/08/2021	30/05/2022	SmPC and PL	
IG/1415	A.7 - Administrative change - Deletion of manufacturing sites	05/08/2021	n/a		
IA/0099/G	This was an application for a group of variations. 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) 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	09/07/2021	n/a		

WS/2086	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.3.z - 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 - Other variation	08/07/2021	30/05/2022	SmPC, Annex II, Labelling and PL	
IG/1387	B.II.c.2.a - Change in test procedure for an excipient - Minor changes to an approved test procedure	18/05/2021	n/a		
N/0096	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	17/05/2021	30/05/2022	PL	
PSUSA/10306 /202010	Periodic Safety Update EU Single assessment - sofosbuvir / ledipasvir	06/05/2021	n/a		PRAC Recommendation - maintenance
IB/0094	B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation	20/11/2020	n/a		
IB/0093/G	This was an application for a group of variations. B.II.b.1.e - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non-sterile medicinal products B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP -	12/11/2020	n/a		

	Replacement/addition of a site where batch control/testing takes place B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place B.II.b.4.b - Change in the batch size (including batch size ranges) of the finished product - Downscaling down to 10-fold				
WS/1915	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 GS-US-248-0123, listed as a category 3 study in the RMP. This is a long-term observational follow-up registry of subjects who did not achieve sustained virologic response in Gilead-sponsored trials in subjects with chronic hepatitis C infection. The RMPs have also been submitted for each of the products in this work-sharing procedure (Harvoni v8.0, Epclusa v7.0 and Vosevi v4.0). C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	29/10/2020	n/a		
IG/1294	A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites	01/10/2020	n/a		

	(excluding manufacturer for batch release)				
IG/1283	B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place	28/08/2020	n/a		
IG/1275	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	18/08/2020	n/a		
X/0081/G	This was an application for a group of variations. Extension application to introduce a new strength (45/200 mg film-coated tablets) and a new pharmaceutical form (coated granules) associated with new strengths (33.75/150 mg and 45/200 mg). The new presentations are indicated for the treatment of chronic hepatitis C (CHC) in adult and paediatric patients aged 3 years and above. The extension application is grouped with a type II variation (C.I.6.a) to include paediatric use in patients aged 3 to < 12 years to the existing presentations of 90/400 mg film-coated tablets. Sections 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated to support the extended indication. Furthermore, sections 5.3 and 6.6 of the SmPC are updated to include new information with regards to	30/04/2020	03/07/2020	SmPC, Labelling and PL	

	the environmental risk assessment of ledipasvir. The RMP (version 7.0) is updated in accordance. In addition, the MAH took the opportunity to implement minor editorial updates and linguistic corrections throughout the Product Information. Annex I_2.(c) Change or addition of a new strength/potency Annex I_2.(d) Change or addition of a new pharmaceutical form C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
IA/0088	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)	20/05/2020	n/a		
IG/1248	C.I.3.a - 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 - Implementation of wording agreed by the competent authority	30/04/2020	03/07/2020	SmPC and PL	
IA/0086/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	30/04/2020	n/a		

	manufacturer of a novel excipient 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 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				
PSUSA/10306 /201910	Periodic Safety Update EU Single assessment - sofosbuvir / ledipasvir	17/04/2020	n/a		PRAC Recommendation - maintenance
IB/0084/G	This was an application for a group of variations. B.II.b.1.e - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non-sterile medicinal products B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place B.II.b.4.b - Change in the batch size (including batch	08/04/2020	n/a		

	size ranges) of the finished product - Downscaling down to 10-fold				
II/0082	Update of section 5.3 of the SmPC in order to add new information on ledipasvir carcinogenicity based on the final results from study TX-256-2016; this was a 104-week oral gavage carcinogenicity study in rats. In addition, the MAH took the opportunity to bring the Product Information in line with the current QRD template version 10.1. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	12/12/2019	03/07/2020	SmPC, Annex II and Labelling	The CHMP considered that ledipasvir was not carcinogenic in the 2-year rat carcinogenicity study (TX-256-2016) at exposures up to 8-times higher than human exposure.
WS/1518	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, 5.1 and 5.2 of the SmPC (Epclusa, Harvoni, Sovaldi) and 4.2, 4.4, 4.8 and 5.2 (Vosevi) in order to add new information regarding the use of the sofosbuvir-containing products in patients with renal impairment, based on final results from studies GS-US-342-4062, GS-US-337-4063 and GS-US-334-0154, listed as a category 3 study in the RMP and study GS-US-338-1125. Study GS-US-342-4062 was a phase 2, multi-centre, open-label study to evaluate the efficacy and safety of sofosbuvir/velpatasvir for 12 Weeks in subjects with chronic HCV infection who are on dialysis for	19/09/2019	29/10/2019	SmPC and PL	Sofosbuvir in a fixed dose combination with ledipasvir was administered for 12 weeks to 18 patients with genotype 1 chronic hepatitis C and severe renal impairment in an open-label study (Study 0154). The safety of sofosbuvir in a fixed dose combination with either ledipasvir or velpatasvir has been studied in 154 patients with ESRD requiring dialysis (Study 4062 and Study 4063). In this setting, exposure of sofosbuvir metabolite GS-331007 is 20-fold increased, exceeding levels where adverse reactions have been observed in preclinical trials. In this limited clinical safety data set, the rate of adverse events and deaths was not clearly elevated from what is expected in ESRD patients. The CHMP considered that safety data on the use of the sofosbuvir-based products in patients with severe renal impairment (estimated glomerular filtration rate [eGFR] <

	end stage renal disease. Study GS-US-337-4063 was a phase 2, multi-centre, open-label study to evaluate the efficacy and safety of ledipasvir/sofosbuvir in subjects with genotype 1, 4, 5 and 6 chronic HCV infection who are on dialysis for end stage renal disease. Study GS-US-334-0154 was a phase 2b, open label study of 200 mg or 400 mg Sofosbuvir+ribavirin for 24 Weeks in Genotype 1 or 3 HCV infected subjects with renal insufficiency. Study GS-US-338-1125 was a phase 1, open-label, parallel-group, single-dose study to evaluate the pharmacokinetics of voxilaprevir in subjects with normal renal function and severe renal impairment. The Package Leaflet is updated accordingly. The RMPs have also been submitted for each of the products in this work-sharing procedure. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				30 mL/min/1.73 m2) and end stage renal disease (ESRD) requiring haemodialysis are limited. Overall, the CHMP concluded that the sofosbuvir-based products can be used in these patients with no dose adjustment when no other relevant treatment options are available.
R/0080	Renewal of the marketing authorisation.	29/05/2019	01/08/2019	SmPC, Annex II and PL	Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of Harvoni in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity. The Product Information has been updated in line with the latest version of the QRD template and in order to revise the timeline for completion of the Annex II post-authorisation safety study

					from Q2 2021 to Q2 2023, as per the final PASS protocol. In addition, the Product Information was updated to reflect on the fact that simeprevir is no longer marketed in the European Union.
PSUSA/10306 /201810	Periodic Safety Update EU Single assessment - sofosbuvir / ledipasvir	29/05/2019	01/08/2019	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10306/201810.
WS/1523	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 in order implement new information on the use of sofosbuvir-based therapy with concomitant drugs, based on final results from study GS-US-334-2130. This was a phase I study to evaluate the effects of cytochrome P450 and drug transporter inducers on sofosbuvir and probe drug pharmacokinetics in healthy subjects. Furthermore, section 4.3 of the Sovaldi SmPC was updated in order to remove the use of rifabutin as a contraindication. The Package Leaflet is updated accordingly. In addition, the Worksharing applicant (WSA) took the opportunity to introduce minor editorial changes throughout the Product Information. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	04/07/2019	29/10/2019	SmPC and PL	Based on results from study GS-US-334-2130, effects of rifabutin and carbamazepine administration on the drug levels of sofosbuvir have been updated throughout the Product Information. With regards to the rifabutin interaction, a 28% reduction in sofosbuvir exposure was observed. Considering that reduction in sofosbuvir dose of <50% is expected to be safe in terms of potentially reduced efficacy, the CHMP concluded that the data support removal of co-administration of rifabutin as contraindication from the Sovaldi (sofosbuvir) Product Information. The contraindication is maintained for Epclusa, Harvoni and Vosevi, given the lack of data on interactions with the other active substances contained in these combination products. The data available for interactions with carbamazepine indicated that sofosbuvir levels were reduced by 48%, but the confidence interval included the 50% value. Therefore, the CHMP considered that a cautionary approach should be taken and contraindication concerning co-administration of carbamazepine should be retained. Furthermore, the term "potent P-glycoprotein inducers" was replaced by "strong P-glycoprotein inducers" throughout the Product Information in line with terminology

					used in the EMA Guideline on the investigation of drug interactions.
IG/1057	B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	01/03/2019	n/a		
IG/1069	C.I.3.a - 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 - Implementation of wording agreed by the competent authority	28/02/2019	06/06/2019	SmPC and PL	
IB/0074/G	This was an application for a group of variations. 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) B.II.f.1.e - Stability of FP - Change to an approved stability protocol	06/02/2019	06/06/2019	SmPC	
IB/0073	B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation	14/01/2019	n/a		
IG/1037	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	14/12/2018	06/06/2019	SmPC and PL	
WS/1476	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.	29/11/2018	n/a		

	Submission of the final report from study GS-US-334-0154, listed as a category 3 study in the RMP. This is a phase 2b randomized, open-label study of 200mg or 400mg sofosbuvir + ribavirin for 24 Weeks in genotype 1 or 3 HCV-infected subjects with renal insufficiency. The RMPs have also been submitted for each of the products in this work-sharing procedure. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				
IA/0069	B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	27/07/2018	n/a		
IB/0068/G	This was an application for a group of variations. A.6 - Administrative change - Change in ATC Code/ATC Vet Code 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)	06/07/2018	06/06/2019	SmPC, Labelling and PL	
T/0067	Transfer of Marketing Authorisation	25/04/2018	07/06/2018	SmPC, Labelling and PL	

II/0064	Update of section 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC in order to update the safety and efficacy information based on interim results from study GS-US-334-0154 listed as a category 3 study in the RMP; this is a study to evaluate the safety, efficacy and pharmacokinetics of treatment with Ledipasvir/Sofosbuvir Fixed-Dose Combination for 12 weeks in Genotype 1 or 4 HCV-Infected Subjects with Renal Insufficiency; the Package Leaflet is updated accordingly. The RMP version 4.0 has also been submitted. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	31/05/2018	06/06/2019	SmPC and PL	No dose adjustment of Harvoni is required for patients with mild or moderate renal impairment. In patients with severe renal impairment and end stage renal disease (ESRD) there is a moderate increase of sofosbuvir and ledipasvir exposure, and a profound increase in the exposure of the main sofosbuvir metabolite. The safety impact of these increases is uncertain. The safety of Harvoni has been assessed in a very limited number of patients with severe renal impairment. For patients with end stage renal disease (ESRD) requiring dialysis there is only scarce data from published case series. Harvoni should only be considered for patients with severe renal impairment/ESRD if no alternative regimens, recommended for this treatment population, can be used for reasons such as concomitant decompensated cirrhosis, or drug interactions that cannot be otherwise handled. When Harvoni is used in patients with severe renal impairment or ESRD, close monitoring of renal function is recommended.
PSUSA/10306 /201710	Periodic Safety Update EU Single assessment - sofosbuvir / ledipasvir	17/05/2018	n/a		PRAC Recommendation - maintenance
WS/1328/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. B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting	08/02/2018	n/a		

	material/intermediate/reagent - Tightening of specification limits				
IB/0065	B.I.d.1.z - Stability of AS - Change in the re-test period/storage period or storage conditions - Other variation	08/01/2018	n/a		
IB/0062/G	This was an application for a group of variations. B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation B.II.f.1.e - Stability of FP - Change to an approved stability protocol	06/12/2017	n/a		
WS/1246/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. 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.d.1.z - Stability of AS - Change in the re-test period/storage period or storage conditions - Other variation	30/11/2017	n/a		
WS/1256	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.	30/11/2017	n/a		

	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				
PSUSA/10306 /201704	Periodic Safety Update EU Single assessment - sofosbuvir / ledipasvir	26/10/2017	n/a		PRAC Recommendation - maintenance
II/0053	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	19/10/2017	07/06/2018	SmPC	Results of the drug interaction study GS-US-337-1887 indicated that there is no relevant effect of ledipasvir on the pharmacokinetics of oral midazolam, a sensitive CYP3A4 substrate. Therefore, no dose adjustments of Harvoni or midazolam are recommended during co-administration. Based on these data and previous interaction data indicating that there are no relevant effects of ledipsavir on the orally administered UGT1A1 substrates raltegravir and dolutegravir, warnings regarding effects of ledipasvir on the exposure to substrates for CYP3A4 and UGT1A1 were removed from the SmPC. Furthermore, warnings concerning CYP2C substrates were also removed as CYP2C enzymes are not intestinally expressed.
IG/0848/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 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	12/10/2017	n/a		

	intermediate used in the manufacture of the AS or manufacturer of a novel excipient				
IB/0058	B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation	20/09/2017	n/a		
IB/0057	B.I.d.1.z - Stability of AS - Change in the re-test period/storage period or storage conditions - Other variation	23/08/2017	n/a		
IB/0056	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)	20/07/2017	07/06/2018	SmPC	
II/0039	Extension of indication to add treatment of chronic hepatitis C in adolescents aged 12 to < 18 years. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated in order to add information on posology, warnings, safety, efficacy and pharmacokinetics. The Package Leaflet and Risk Management Plan (RMP version 2.1) are updated in accordance. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	22/06/2017	19/07/2017	SmPC and PL	Please refer to the Scientific Discussion Harvoni EMEA/H/C/003850/II/0039.
WS/1163	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.	06/07/2017	n/a		

	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation				
II/0052	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	15/06/2017	n/a		
IB/0054	B.I.d.1.z - Stability of AS - Change in the re-test period/storage period or storage conditions - Other variation	13/06/2017	n/a		
II/0035	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	21/04/2017	24/05/2017	SmPC and PL	Based on the assessment of data from two clinical studies evaluating efficacy and safety of Harvoni + ribavirin in subjects infected with chronic hepatitis C (HCV) who have advanced liver disease, the CHMP concluded that in situations where the dose of ribavirin is low due to tolerability reasons, a prolonged treatment (24 weeks) with Harvoni + ribavirin should be considered to minimise the risk of relapse. Furthermore, in genotype 3 infection, the use of Harvoni (always in combination with ribavirin) should only be considered for patients who are deemed at high risk of clinical disease progression and who do not have alternative treatment options.
II/0049	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	11/05/2017	19/07/2017	SmPC and PL	Based on the assessment of post-marketing safety data on Harvoni, the CHMP considered that the following information should be added in the Product Information: "Other effects that may be seen during treatment with Harvoni

					The frequency of the following side effects is not known (frequency cannot be estimated from the available data). • Swelling of the face, lips, tongue or throat (angioedema).”
PSUSA/10306 /201610	Periodic Safety Update EU Single assessment - sofosbuvir / ledipasvir	05/05/2017	n/a		PRAC Recommendation - maintenance
IB/0050/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 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.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	06/04/2017	n/a		

WS/1075	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	23/03/2017	n/a		
II/0046	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	23/02/2017	n/a		
A20/0027	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 whether the marketing authorisation of these products should be maintained, varied, suspended or revoked.	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
WS/1104	This was an application for a variation following a	16/02/2017	n/a		

	worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation				
IB/0044/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.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.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.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.a - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The	21/12/2016	n/a		

	proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation				
IB/0042	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)	08/12/2016	23/02/2017	SmPC	
IAIN/0045	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	28/11/2016	23/02/2017	SmPC and PL	
IA/0041	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	25/11/2016	n/a		
WS/1035/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. 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.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other	10/11/2016	n/a		

	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.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation				
IA/0040	A.7 - Administrative change - Deletion of manufacturing sites	09/11/2016	n/a		
PSUSA/10306 /201604	Periodic Safety Update EU Single assessment - sofosbuvir / ledipasvir	27/10/2016	n/a		PRAC Recommendation - maintenance
IG/0725	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	21/10/2016	n/a		
WS/1008	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits	06/10/2016	n/a		
II/0033	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance	15/09/2016	23/02/2017	SmPC	Section 4.4 of the SmPC has been updated as follows: HCV/HBV (hepatitis B virus) co infection

	data				There are limited no data on the use of Harvoni in patients with HCV/HBV co infection.
WS/0980/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. 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.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.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	15/09/2016	n/a		
PSUSA/10306 /201510	Periodic Safety Update EU Single assessment - sofosbuvir / ledipasvir	26/05/2016	22/07/2016	SmPC and PL	Please refer to Harvoni PSUSA-00010306-201510 EPAR: Scientific conclusions and grounds recommending the variation to the terms of the marketing authorisation.
II/0030	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	21/07/2016	n/a		
WS/0941	This was an application for a variation following a worksharing procedure according to Article 20 of	23/06/2016	n/a		

	Commission Regulation (EC) No 1234/2008. 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				
IB/0028/G	This was an application for a group of variations. A.6 - Administrative change - Change in ATC Code/ATC Vet Code C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	07/04/2016	02/05/2016	SmPC and PL	
WS/0904/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. 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.z - Quality change - Active substance - Other variation 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	07/04/2016	n/a		

	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.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.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.a.2.b - Changes in the manufacturing process of the AS - Substantial change to the manufacturing process of the AS which may have a significant impact on the quality, safety or efficacy of the medicinal product				
IA/0026	B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	31/03/2016	n/a		
IB/0025	B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation	22/03/2016	n/a		
IA/0023/G	This was an application for a group of variations.	15/02/2016	n/a		

	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure				
IG/0624	A.7 - Administrative change - Deletion of manufacturing sites	11/01/2016	n/a		
II/0013	Update of sections 4.2, 4.4 and 5.1 of the SmPC in order to include data on the treatment of non-genotype 1 HCV-infected subjects. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	19/11/2015	18/12/2015	SmPC	In this application the MAH presented data from 4 studies where patients with genotype 2-, 4-, 5- and 6- hepatitis C-infection were treated with sofosbuvir/ledipasvir (without ribavirin) for a duration of 12 weeks. All studies were of limited size with low number of cirrhotic patients. Sustained virologic response at 12 weeks following completion of all treatment (SVR12) was achieved by >90% of the patients across the studies. When bridging efficacy from such limited studies to large scales studies performed in genotype-1 infected patients, both subtypes (within the different genotypes) and naturally occurring polymorphisms with potential impact on ledipasvir susceptibility (sofosbuvir being convincingly pangenotypic) must be taken into account. For genotype 2, there is presently not enough data to support a general recommendation of Harvoni for the treatment of chronic HCV infection caused by this genotype. Specifically, there is not enough data to support that sofosbuvir/ledipasvir (without ribaivirin) is an optimized regimen regardless of the naturally occurring

					NS5A polymorphism L31M. That polymorphism, which substantially lowers the in vitro susceptibility to ledipasvir, is seen in a round 50% of genotype 2 isolates from untreated patients. For genotype 4, in vitro data for ledipasvir and clinical data for the combination were presented for a high variety of genotype 4 subtypes. The issue of naturally occurring polymorphisms were also taken into account. This data support the use of sofosbuvir/ledipasvir also in less frequently studied genotype 4 subtypes (outside 4a and d, such as 4r). Specific patterns of multiple polymorphisms, seen very unfrequently, rather than subtype were associated with lowered in vitro susceptibility with consequent potential loss of efficacy. For genotype-5 infection, the limited clinical data in combination with the high in vitro susceptibility for ledipasvir (as well as sofosbuvir) justifies an extrapolation of results obtained in genotype-1 infected patients and to include treatment recommendation and duration in section 4.2. For genotype 6, data from genotype 6a and 6e had been presented at the time of approval, where the ledipasvir susceptibility is considerably lower for 6e than for 6a. As part of this application, extensive in vitro data for other rare subtypes was presented, where the in vitro susceptibility to ledipasvir were lower than that seen for subtype 6a, in line with that for 6e. However, sofosbuvir/ledipasvir given for 12 weeks (without ribavirin) yielded the same very high cure rates in patients infected with such subtypes. Although numbers are limited, the data are considered as convincing evidence to include treatment recommendation and duration in section 4.2, in light of the

					lack of other IFN-free alternatives.
WS/0841/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. 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.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.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	10/12/2015	n/a		
IA/0020/G	This was an application for a group of variations. B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	20/11/2015	n/a		
IB/0019/G	This was an application for a group of variations.	19/11/2015	n/a		

	B.II.b.1.e - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non-sterile medicinal products B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place B.II.b.4.b - Change in the batch size (including batch size ranges) of the finished product - Downscaling down to 10-fold				
PSUSA/10306 /201504	Periodic Safety Update EU Single assessment - sofosbuvir / ledipasvir	06/11/2015	n/a		PRAC Recommendation - maintenance
II/0004	Update of sections 4.2 and 5.1 of the SmPC in light of emergent data from Study GS-US-337-0121 (SIRIUS). 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	24/09/2015	28/10/2015	SmPC and PL	The MAH has submitted results of SIRIUS study which shown that sofosbuvir/ledipasvir (Harvoni) in combination with weight based ribavirin given for 12 weeks is a highly efficacious regimen for the treatment of cirrhotic genotype-1 infected patients, with results similar to those achieved with ledipasvir/sofosbuvir (without ribavirin) given for 24 weeks. Update sections 4.2 and 5.1 of the SmPC based on the results of GS-US-337-0121 study.
II/0017	Update of section 5.3 of the SmPC in order to update preclinical information on carcinogenicity in mice	22/10/2015	18/12/2015	SmPC	Ledipasvir was not carcinogenic in the 6 month rasH2 transgenic mouse study at exposures up to 26 fold higher

	based on the results from study TX-256-2019 (A 26-Week Oral Gavage Carcinogenicity and Toxicokinetic Study with GS-5885 in RasH2 Mice) C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				than human exposure. A carcinogenicity study in rats is ongoing.
II/0012	Update of section 5.1 of the SmPC in order to include data on patients who have previously failed treatment on a sofosbuvir/ribavirin ± pegylated interferon treatment regimen. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	24/09/2015	28/10/2015	SmPC	
II/0011	Update of section 5.1 of the SmPC in order to add data from study GS-US-337-0115 (ION-4) on outcomes with sofosbuvir/ledipasvir (without ribavirin) given for 12 weeks to HCV/HIV co-infected patients with hepatitis C genotype-1 or -4 infection. In addition, the number of patients included in clinical studies with ledipasvir/sofosbuvir is being updated in section 5.2 of the SmPC. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	24/09/2015	28/10/2015	SmPC	
II/0005	Update of sections 4.2, 4.4, 4.8 and 5.1 of the SmPC	24/09/2015	28/10/2015	SmPC	Interim data of the SOLAR study was provided within the

	in light of emergent data from Study GS-US-337-0123 (SOLAR-1). C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				approval procedure of Harvoni. The MAH has provided data that includes SVR12 for all patients in both treatment arms. Update of sections 4.2, 4.4, 4.8 and 5.1 of the SmPC in light of emergent data from Study GS-US-337-0123 (SOLAR-1). The package leaflet has been amended accordingly to reflect changes in the SmPC.
IB/0014	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	20/08/2015	n/a		
IG/0599	B.I.c.2.b - Change in the specification parameters and/or limits of the immediate packaging of the AS - Addition of a new specification parameter to the specification with its corresponding test method	12/08/2015	n/a		
IG/0595	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	04/08/2015	n/a		
IG/0583	A.7 - Administrative change - Deletion of manufacturing sites	23/07/2015	n/a		
IB/0008	To extend the shelf-life of the Ledipasvir Spray-Dried Dispersion (LDV SDD) intermediate from 6 months to 15 months. The applicant took the opportunity to make editorial corrections to section 3.2.P.3.4, 3.2.P.8.1 and 3.2.P.8.3: • Correction of the reference of the	09/07/2015	n/a		

	Identification by IR spectroscopy from Ph. Eur. 2.2.25 to Ph. Eur. 2.2.24 • Correction in Section 7.1 of the corporate test method, TM-221: Residual Solvents in Ledipasvir Spray-Dried Dispersion, Bulk Powder, by Headspace Gas Chromatography, of the lower limit for the detection of solvents (ethanol and acetone) from 0.05% to 0.005% • Reordering of existing information, alignment of information among the sections, punctuation changes and grammatical corrections B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation				
IB/0007	C.I.3.a - 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 - Implementation of wording agreed by the competent authority	22/06/2015	28/10/2015	SmPC and PL	
IB/0006/G	This was an application for a group of variations. B.I.a.2.z - Changes in the manufacturing process of the 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.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	19/06/2015	n/a		

	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.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.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation A.7 - Administrative change - Deletion of manufacturing sites				
WS/0725/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. 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.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	21/05/2015	n/a		

	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.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation				
IG/0521	A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release	26/02/2015	28/10/2015	Annex II and PL	
IG/0525/G	This was an application for a group of variations. 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.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.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	02/02/2015	n/a		