Sovaldi

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				
N/0080	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	19/08/2022		PL	
PSUSA/10134 /202112	Periodic Safety Update EU Single assessment - sofosbuvir	07/07/2022	n/a		PRAC Recommendation - maintenance
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/0079	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/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	
IG/1415	A.7 - Administrative change - Deletion of manufacturing sites	05/08/2021	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	
PSUSA/10134 /202012	Periodic Safety Update EU Single assessment - sofosbuvir	08/07/2021	n/a		PRAC Recommendation - maintenance
IB/0074	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)	25/06/2021	30/05/2022	SmPC 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/0070	Minor change in labelling or package leaflet not	17/05/2021	30/05/2022	PL	

	connected with the SPC (Art. 61.3 Notification)				
IB/0072	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	11/05/2021	n/a		
IB/0068	B.II.c.2.d - Change in test procedure for an excipient - Other changes to a test procedure (including replacement or addition)	20/11/2020	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 (excluding manufacturer for batch release)	01/10/2020	n/a		
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		
PSUSA/10134 /201912	Periodic Safety Update EU Single assessment - sofosbuvir	09/07/2020	n/a		PRAC Recommendation - maintenance
X/0059/G	This was an application for a group of variations. Extension application to introduce a new strength	30/04/2020	25/06/2020	SmPC, Annex II, Labelling and PL	

	(200 mg film-coated tablets) and a new pharmaceutical form (coated granules) associated with new strengths (150 and 200 mg). The new presentations are indicated in combination with other medicinal products 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 400 mg film-coated tablets. Sections 4.2, 4.8, 5.1 and 5.2 of the SmPC and the Package Leaflet are updated to support the extended indication. The RMP (version 10.0) 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				
IG/1247	A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites	08/05/2020	n/a		

	(excluding manufacturer for batch release)				
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	25/06/2020	SmPC and PL	
IA/0062/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 intermediate used in the manufacture of the AS or manufacturer of a novel excipient	30/04/2020	n/a		
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-	19/09/2019	21/10/2019	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

	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 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				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] < 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.
PSUSA/10134 /201812	Periodic Safety Update EU Single assessment - sofosbuvir	27/06/2019	23/08/2019	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for

					PSUSA/10134/201812.
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	21/10/2019	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.
IB/0058/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	28/03/2019	23/08/2019	SmPC	

	(supported by real time data) B.II.f.1.e - Stability of FP - Change to an approved stability protocol				
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/1037	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	14/12/2018	23/08/2019	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. 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	29/11/2018	n/a		
R/0050	Renewal of the marketing authorisation.	26/07/2018	17/09/2018	SmPC, Annex II, Labelling	Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of

				and PL	Sovaldi in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.
PSUSA/10134 /201712	Periodic Safety Update EU Single assessment - sofosbuvir	28/06/2018	23/08/2018	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10134/201712.
T/0051	Transfer of Marketing Authorisation	25/04/2018	06/07/2018	SmPC, Labelling and PL	
II/0048	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	15/03/2018	n/a		
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 material/intermediate/reagent - Tightening of specification limits	08/02/2018	n/a		
PSUSA/10134 /201706	Periodic Safety Update EU Single assessment - sofosbuvir	11/01/2018	n/a		PRAC Recommendation - maintenance

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. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	30/11/2017	n/a		
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	12/10/2017	n/a		

	or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient				
II/0036	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 5.2) are updated in accordance. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet. Furthermore, the Product Information is brought in line with the latest QRD template version 10. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	20/07/2017	14/09/2017	SmPC, Annex II, Labelling and PL	Please refer to the Scientific Discussion Sovaldi EMEA/H/C/002798/II/0036.
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)	06/07/2017	14/09/2017	SmPC	
WS/1163	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	06/07/2017	n/a		

	obligations and conditions of a marketing authorisation, including the RMP - Other variation				
PSUSA/10134 /201612	Periodic Safety Update EU Single assessment - sofosbuvir	06/07/2017	n/a		PRAC Recommendation - maintenance
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		
A20/0029	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 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	16/02/2017	n/a		
PSUSA/10134 /201606	Periodic Safety Update EU Single assessment - sofosbuvir	12/01/2017	n/a		PRAC Recommendation - maintenance
IG/0748	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	28/11/2016	23/02/2017	SmPC and PL	
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 variation B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	10/11/2016	n/a		

	B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation				
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		
PSUSA/10134 /201512	Periodic Safety Update EU Single assessment - sofosbuvir	21/07/2016	19/09/2016	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10134/201512.
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	15/09/2016	n/a		

	B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation				
WS/0941	This was an application for a variation following a worksharing procedure according to Article 20 of 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	23/06/2016	n/a		
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 B.I.a.1.a - Change in the manufacturer of AS or of a	07/04/2016	n/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				
II/0018	In order to address MEA 003, submission of the final study report GS-US-334-1344 to evaluate the pharmacokinetic drug-drug interaction between sofosbuvir and rifampicin. Following the review of the study result, section 4.3 of the SmPC was updated to add a contraindication for use with potent P-gp inducers. Sections 4.4 and 4.5 of the SmPC were also updated section 4.5 and the PL was updated accordingly.	17/12/2015	28/01/2016	SmPC and PL	

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
PSUSA/10134 /201506	Periodic Safety Update EU Single assessment - sofosbuvir	14/01/2016	n/a		PRAC Recommendation - maintenance
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		
II/0015	Submission of the final study report to investigate the safety and efficacy of GS-7977 and ribavirin for 24 weeks in subjects with recurrent chronic HCV post liver transplant (GS-US-334-0126). Following the CHMP discussions, section 4.2 of the SmPC is	22/10/2015	15/01/2016	SmPC	

	updated to include information relating to the appropriate ribavirin starting dose for the post-liver transplant population, sections 4.8 and 5.1 are updated accordingly. The submission of this study fulfils MEA 005. An updated RMP (version 3.3) is agreed. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				
IG/0614	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	02/10/2015	n/a		
IB/0021	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)	14/08/2015	15/01/2016	SmPC	
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	23/07/2015	n/a		

	manufacturing sites				
IB/0019	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	15/01/2016	SmPC and PL	
PSUSA/10134 /201412	Periodic Safety Update EU Single assessment - sofosbuvir	11/06/2015	n/a		PRAC Recommendation - maintenance
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 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	21/05/2015	n/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	27/05/2015	Annex II and PL	
II/0011	Submission of the study report AD-334-2027 (formerly P7977-2025-LPK) in order to fulfil MEA 004 - Determination of nucleotide analogue levels in liver explants from HCV infected subjects undergoing liver transplant following treatment with sofosbuvir and ribavirin. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	26/02/2015	n/a		This variation lead to no changes in the product information or the RMP.
IA/0013	A.6 - Administrative change - Change in ATC Code/ATC Vet Code	25/02/2015	27/05/2015	SmPC	
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	02/02/2015	n/a		

	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				
PSUV/0009	Periodic Safety Update	09/01/2015	n/a		PRAC Recommendation - maintenance
II/0010/G	This was an application for a group of variations. 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	18/12/2014	n/a		
II/0006	Update of section 5.2 of the SmPC to reflect the results of the pre-clinical study AD-334-2024. The provision of the final study report for study AD-334-2024 addresses MEA 012. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	20/11/2014	27/05/2015	SmPC	The scope of this variation is to provide the final study report for pre-clinical study AD-334-2024, in order to fulfil the post-authorisation measure MEA 012. MEA is a commitment that was agreed during the CHMP assessment of the initial marketing authorisation application for Sovaldi. Study AD-334-2024 - In Vitro Inhibition Studies of Pgp, OCT1, OCT2, MATE1, OAT3, BSEP and MRP2 Transporters by High Concentrations of GS-331007 (Nucleoside Metabolite of Sofosbuvir). This study was requested by the CHMP to provide an additional analysis of the potential for pharmacokinetic

					drug-drug interactions of GS-331007, the predominant metabolite of SOF in plasma and excreta, with human Pgp, OCT1, OCT2, MATE1, OAT3, BSEP and MRP2 transporters. The CHMP concluded that Sofosbuvir is not a substrate for hepatic uptake transporters, organic anion transporting polypeptide (OATP) 1B1 or 1B3, and organic cation transporter (OCT) 1. While subject to active tubular secretion, GS 331007 is not a substrate for renal transporters including organic anion transporter (OAT) 1 or 3, OCT2, MRP2, P gp, BCRP or MATE1. Sofosbuvir and GS 331007 are not inhibitors of drug transporters P gp, BCRP, MRP2, BSEP, OATP1B1, OATP1B3 and OCT1. GS 331007 is not an inhibitor of OAT1, OCT2, and MATE1.
II/0007	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	25/09/2014	n/a		
IG/0469	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	07/08/2014	n/a		
II/0002/G	This was an application for a group of variations. Grouping of 4 variations with the submission of the final study reports for the following non clinical studies submitted in fulfilment of post-authorisation commitments for additional analysis of the potential for pharmacokinetic drug-drug interactions of sofosbuvir mediated by cytochrome P450 enzymes	26/06/2014	27/05/2015	SmPC	The final study reports for the following non clinical studies were submitted in fulfilment of post-authorisation commitments for additional analysis of the potential for pharmacokinetic drug-drug interactions of sofosbuvir mediated by cytochrome P450 enzymes (study AD-334-2020), OAT1 transporter (study AD-334-2021), UGT1A1 enzyme (study AD-334-2022) and Pgp transporter (study AD-334-2023). The product information was updated

	(study AD-334-2020 – MEA008), OAT1 transporter (study AD-334-2021 – MEA009), UGT1A1 enzyme (study AD-334-2022 – MEA010) and Pgp transporter (study AD-334-2023 – MEA011). Update of section 5.2 of the SmPC with the results from studies AD-334-2020, AD-334-2021 and AD-334-2022. Corrections were also made to the sections 4.2, 4.5, 5.1, 5.2 of the SmPC. 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				accordingly. The CHMP concluded that the MEAs 009, 10 and 11 were fulfilled. However, the CHMP considered that MEA008 was not fulfilled as mechanism based inhibition for CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6 should also be investigated.
IB/0005	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	06/06/2014	n/a		
IB/0003/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	22/05/2014	n/a		

	variation B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation				
IA/0004	B.II.f.1.e - Stability of FP - Change to an approved stability protocol	21/05/2014	n/a		
IG/0422	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	28/03/2014	n/a		