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
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		

[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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	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 obligations and conditions of a marketing	06/07/2017	n/a		

	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 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				
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 B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other	15/09/2016	n/a		

	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 starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved	07/04/2016	n/a		

	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. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	17/12/2015	28/01/2016	SmPC and PL	

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 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.	22/10/2015	15/01/2016	SmPC	

	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 manufacturing sites	23/07/2015	n/a		
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	22/06/2015	15/01/2016	SmPC and PL	

	wording agreed by the competent authority				
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 starting material/reagent/intermediate for AS - Other variation	21/05/2015	n/a		
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 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		
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 (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.	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 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.

	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				
IB/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 variation B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation	22/05/2014	n/a		
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	28/03/2014	n/a		

	PSMF location				