EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

OLYSIO

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
PSUSA/10255 /201705	Periodic Safety Update EU Single assessment - simeprevir	14/12/2017	08/02/2018	SmPC	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10255/201705.
IA/0033	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)	28/07/2017	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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II/0031	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	20/07/2017	11/01/2018	SmPC	
PSUSA/10255 /201611	Periodic Safety Update EU Single assessment - simeprevir	09/06/2017	n/a		PRAC Recommendation - maintenance
N/0032	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	24/03/2017	11/01/2018	PL	
IA/0030	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	16/03/2017	n/a		
A20/0019	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

II/0027/G	This was an application for a group of variations. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	19/01/2017	11/01/2018	SmPC	
IB/0028	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	09/12/2016	23/02/2017	SmPC and PL	
N/0026	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	09/12/2016	23/02/2017	Labelling and PL	
PSUSA/10255 /201605	Periodic Safety Update EU Single assessment - simeprevir	01/12/201	n/a		PRAC Recommendation - maintenance
IB/0025/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.III.1.b.2 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability -	1[illegible]/2016	23/02/2017	SmPC	

	Updated certificate from an already approved manufacturer B.III.1.b.4 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Deletion of certificates (in case multiple certificates exist per material) B.III.1.b.2 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer B.III.1.b.2 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer				
PSUSA/10255 /201511	Periodic Safety Update EU Single assessment - simeprevir	23/06/201[illegible]	18/08/2016	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10255/201511.
IA/0023	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	14/07/2016	n/a		
II/0021	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	07/07/2016	n/a		
II/0015	Update of sections 4.2, 4.4, 4.5, 4.8 and 5.1 of the	26/05/2016	30/06/2016	SmPC,	The current product information for OLYSIO includes a

	SmPC in order to amend the safety information regarding the use of Olysio in interferon-free regimens, based on the primary analysis (SVR12) of studies HPC3017 and HPC3018. The Package Leaflet and Labelling are updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data			Labelling and PL	recommendation for the interferon-free regimen combining simeprevir and sofosbuvir (SMV+SOF) with or without ribavirin which is based on the results of the COSMOS study and real-world clinical practice data. In this application, data from the Phase 3 studies TMC435 HPC3017/OPTIMIST-1 and TMC435 HPC3018/OPTIMIST-2 are presented and the MAH proposed to updated sections 4.4, 4.4, 4.5, 4.8 and 5.1 according to the results of these studies. Data submitted confirms the efficacy of the combination given 12 weeks (without RBV) in patients without cirrhosis and shows that 8 week is clearly inferior to the 12 weeks regimen and that does not provide maximal efficacy. In cirrhotic patients, data submitted showed lower efficacy in cirrhotic patients when this regimen is given 12 weeks without RBV. Therefore, this regimen cannot be generally recommended in cirrhotic patients. A 12-weeks regimen may be considered for [cirrhotic] patients deemed at low risk for clinical disease progression and who have subsequent retreatment options.
IB/0020	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	09/06/2016	n/a		
II/0017	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	28/01/2016	30/06/2016	SmPC and Annex II	
IA/0016	B.I.a.3.a - Change in batch size (including batch size ranges) of AS or intermediate - Up to 10-fold	10/12/2015	n/a		

	increase compared to the originally approved batch size				
PSUSA/10255 /201505	Periodic Safety Update EU Single assessment - simeprevir	03/12/2015	n/a		PRAC Recommendation - maintenance
PSUSA/10255 /201411	Periodic Safety Update EU Single assessment - simeprevir	25/06/2015	20/08/2015	SmPC, Labelling and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10255/201411.
II/0011	Update of sections 4.5 and 5.2 of the SmPC in order to add new preclinical data on the in vitro inhibitory potential of simeprevir on human OCT2, BCRP and OATP1B3. In addition, a minor change was introduced in section 5.1 of the SmPC. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	23/07/2015	30/06/2016	SmPC	
II/0008	Update of sections 4.2, 4.8 and 5.2 of the SmPC in order to add information on the use of the product in East Asian patients based on the results of the HPC3005 study. Minor editorial amendments are introduced in section 5.1 of the SmPC. The Package Leaflet is updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	23/07/2015	30/06/2016	SmPC and PL	
II/0004/G	This was an application for a group of variations.	23/07/2015	n/a		

	B.II.d.1.e - Change in the specification parameters and/or limits of the finished product - Change outside the approved specifications limits range B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.f.1.e - Stability of FP - Change to an approved stability protocol				
II/0012	Update of sections 4.2 and 4.4 of the SmPC in order to remove information limiting the use of IFN-free therapy with Olysio to patients who are intolerant to, or ineligible for, IFN therapy and are in urgent need of treatment. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	25/06/2015	20/08/2015	SmPC	
II/0007/G	This was an application for a group of variations. Update of section 4.5 of the SmPC in order to inform prescribers that co administration of simeprevir with ledipasvir is not recommended while no dose adjustment is needed when simeprevir is given concomitantly with dolutegravir. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to	25/06/2015	20/08/2015	SmPC and PL	

	new quality, preclinical, clinical or pharmacovigilance data				
IB/0010/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.d.2.b - Change in test procedure for the finished product - Deletion of a test procedure if an alternative method is already authorised	07/05/2015	n/a		
IG/0531	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	05/03/2015	n/a		
II/0003	Update of section 4.2 of the SmPC in order to adjust to≥25 IU/ml the HCV RNA threshold for the treatment stopping rule at week 12 and week 24. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	26/02/2015	20/08/2015	SmPC	Treatment stopping rules in patients receiving OLYSIO in combination with peginterferon alfa and ribavirin with inadequate on-treatment virologic response have been updated after analyses of data obtained using samples from the clinical studies which have indicated same HCV RNA threshold for all the time points of treatment. As a consequence, treatment with peginterferon alfa and ribavirin should be discontinued at treatment week 12 or 24 when the HCV RNA load is ≥ 25 IU/ml.
IA/0006	B.I.c.1.a - Change in immediate packaging of the AS - Qualitative and/or quantitative composition	10/02/2015	n/a		
II/0002	Update of sections 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC in order reflect the final result of studies C212 (co-infected), HPC3012 (Genotype 4), HP2002 (Cosmos study). In addition, some editorial changes	22/01/2015	20/08/2015	SmPC and PL	

	are included. Package leaflet and labelling are updated in accordance. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
II/0001	Update of sections 4.4 and 4.5 of the SmPC in order reflect a recommendation not to combine simeprevir and ciclosporin in organ transplant patients and information on interactions and dose recommendation when simeprevir is co-administered with other immunosuppressants. In addition, minor editorial changes have been introduced throughout the PI. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	18/12/2014	20/08/2015	SmPC	The current update of the Product Information reflects the interim analysis of the preliminary PK data from the Phase 2, Open-Label Study to Investigate the Pharmacokinetics, Efficacy, Safety, and Tolerability of the Combination of Simeprevir (TMC435), Daclatasvir (BMS-790052) and Ribavirin (RBV) in Patients with Recurrent Chronic Hepatitis C Genotype 1b Infection after Orthotopic Liver transplantation (preliminary pharmacokinetic analysis of simeprevir and daclatasavir plasma concentrations of Part 1). The planned analysis showed on average 5-times higher simeprevir plasma exposures in subjects with fibrosis receiving cyclosporin (CsA). Therefore the MAH proposed an update of sections 4.4 and 4.5 of the SmPC in order reflect a recommendation not to combine simeprevir and ciclosporin in organ transplant patients and information on interactions and dose recommendation when simeprevir is co-administered with other immunosuppressants.