EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

INCIVO

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
II/0035	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	25/06/2015		SmPC, Annex II and PL	
II/0037	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	21/05/2015	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/0030	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		
II/0034	Update of sections 4.2, 4.4, 4.8 and 5.1 of the SmPC in in order to reflect the results of study VX-950HPC3008 in HCV/HIV co-infected patients. In addition, the MAH took the opportunity to substitute the word 'subjects' for 'patients' in the description of the C211 study description 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	18/12/2014	22/01/2015	SmPC and PL	In this type II variation the product information of Incivo has been updated to include the results of the Phase 3b Study VX-950HPC3008 (Study HPC3008) in hepatitis C virus (HCV) treatment naïve and treatment-experienced subjects with genotype 1 chronic hepatitis C and human immunodeficiency virus type 1 (HCV-1/HIV-1) co-infection.
IB/0036	B.II.f.1.z - Stability of FP - Change in the shelf-life or storage conditions of the finished product - Other variation	07/01/2015	n/a		
II/0033	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	18/12/2014	n/a		
PSUV/0028	Periodic Safety Update	23/10/2014	16/12/2014	SmPC and Labelling	Please refer to Incivo PSUV-28 EPAR: Scientific conclusions and grounds recommending the variation to the terms of the marketing authorisation.
IB/0032	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	28/10/2014	n/a		

II/0026/G	This was an application for a group of variations. A group of two type II variations to update sections 4.5 and 5.2 of the SmPC to reflect the results of 2 in vitro studies. One study to investigate the potential induction of CYP1A2, 2B6, 2C19 and 3A4 by telaprevir and its isomer in human hepatocytes and another study to investigate the inhibition of SLC22A2 (OCT2), SLC47A1 (MATE1) and SLC47A2 (MATE2-K) by telaprevir and its isomer. 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	24/07/2014	16/12/2014	SmPC	The MAH has submitted a group of two type II variations to reflect in the SmPC the results of 2 in vitro studies. Study FK10400 investigated the potential induction of CYP1A2, 2B6, 2C19 and 3A4 by telaprevir and its isomer VRT-127394 in human hepatocytes and study FK10489 to investigate the inhibition of SLC22A2 (OCT2), SLC47A1 (MATE1) and SLC47A2 (MATE2-K) by telapravir and VRT-127394. Results do not show a relevant inhibition by telaprevir of the organic cation transporter (OCT) OCT2. Telaprevir is a weak in vitro inhibitor of the transporters multidrug and toxin extrusion (MATE) MATE1 and MATE2 K with an IC50 of 28.3 µM and 32.5 µM, respectively. The clinical implications of this finding are currently unknown and this information is refected in the SmPC. Telaprevir may potentially increase plasma concentrations of medicinal products in which excretion is dependent upon multidrug and toxin extrusion (MATE) 1 and MATE2 K. the interaction with metformin was reflected on table 2 on the interactions with other medicinal products. Close monitoring of metformin efficacy and safety is recommended when starting or stopping INCIVO in patients receiving metformin. A dose adjustment of metformin may be necessary.
IB/0029	C.I.11.z - Introduction of, or change(s) in, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	09/07/2014	n/a		
PSUV/0024	Periodic Safety Update	25/04/2014	19/06/2014	SmPC	Please refer to: H-2313-PSUV-24 “Scientific conclusions and grounds recommending the variation to the terms of the marketing authorisation.”

II/0027	The MAH provides the report of the survey of the medical education program amongst HCV treating physicians to mitigate the risk for rash and severe cutaneous adverse reactions (SCARs). This survey is a requirement as laid down in the RMP. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	25/04/2014	n/a		The company has evaluated the awareness of Incivo associated dermatological effects and of the Incivo Rash Education Program through an online survey with 415 Incivo-prescribing physicians. The results suggest a generally good understanding of the risks and management of Incivo-associated skin events. A second wave survey is planned 18 months after the conduct of the presently reported survey.
II/0022	Update of sections 4.2 and 4.4 of the SmPC with a description of decompensated liver disease, information on the laboratory parameter albumin and a warning regarding anemia in patients with advanced liver disease. The changes were made at the request of CHMP further to the assessment of PSUR 3. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	20/03/2014	19/06/2014	SmPC	A review of available data on the use of telaprevir, in combination with peginterferon and ribavirin, in patients with cirrhosis did not find evidence that telaprevir contributes to mortality in such patients. However as a precautionary measure the product information is updated to provide further clarification of the concept of decompensated liver disease, as well as to include a recommendation not to use telaprevir based triple therapy if albumin is <3.3 g/L. In addition a further warning is added to section 4.4 to emphasize that close monitoring and early management of adverse events are recommended when INCIVO is used in patients with advanced liver disease.
IB/0025	B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	06/02/2014	n/a		
PSUV/0021	Periodic Safety Update	24/10/2013	18/12/2013	SmPC and PL	Please refer to: H-2313-PSUV-21 "Scientific conclusions and grounds recommending the variation to the terms of the marketing authorisation."
II/0019	Section 4.5 of the SmPC is updated with the results of a drug drug interaction study with the	18/12/2013	19/06/2014	SmPC and PL	The results of the drug drug Interaction study VX-950HPC1002 showed that the anticonvulsant drugs

	antiepileptics Phenytoin and Carbamazepine further to a request of the CHMP made in the context of the assessment of MEA 017. A minor wording correction is also implemented in section 4.4 of the SmPC. Furthermore, a minor update has been made to the PL. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				carbamazepine and phenytoin reduce telaprevir exposure. Due to a similar mechanism, phenobarbital may also reduce telaprevir concentrations. The data has been reflected in the SmPC.
IB/0020	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	17/10/2013	31/10/2013	SmPC and PL	To implement class labeling onthe contra-indication on the concomitant use of quetiapine and Incivo to update the Product Information for INCIVO (SmPC sections 4.3, 4.5, and the corresponding section in the PL). In addition the MAH took the opportunity within this variation to update the Product Information according to QRD template version 9.0 to include the black symbol and explanatory statements indicating the product is subject to additional monitoring. Furthermore, the MAH seized the opportunity to update its representatives' contact list for: Belgium, Luxembourg, Czech Republic, Hungary, Norway, France, Portugal, Romania, Ireland, Iceland, Cyprus and Latvia.
IB/0016	B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate	20/09/2013	n/a		
IB/0017	B.I.d.1.a.4 - Stability of AS - Change in the re-test period/storage period - Extension or introduction of a	15/08/2013	n/a		

	re-test period/storage period supported by real time data				
N/0015	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	02/08/2013	31/10/2013	PL	Inclusion of additional local representative of the MAH for the new member state Croatia.
IG/0341	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	31/07/2013	n/a		
II/0014	Update of sections 4.2, 4.5, 4.8, 5.1 and 5.2 of the SmPC with a twice daily dosing regimen for telaprevir instead of every 8 hours. The PL is updated accordingly. In addition, the meaning of "undetectable" (i.e. target not detected) was specified in sections 4.2 and 5.1 the SmPC C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	25/04/2013	27/05/2013	SmPC and PL	Study C211 was a randomised, open-label, Phase 3 study conducted in treatment naïve patients who were randomised to one of two treatment groups: Incivo 750 mg every 8 hours or Incivo 1125 mg twice daily in combination with peginterferon alfa-2a and ribavirin. The primary objective was to demonstrate the non-inferiority of twice over thrice daily regimen. The SVR12 rate for the twice daily group was 74% (274/369) compared to 73% (270/371) in the thrice daily group with 95% confidence interval of the difference: 4.9%, 12.0% . The lower limit of the 95% CI (4.9%) was greater than the pre-determined noninferiority margin of 11% and therefore the non inferiority of twice over thrice daily regimen was demonstrated. The safety profile of combination therapy with Incivo 1125 mg twice daily was similar to the safety profile for patients receiving combination therapy with Incivo 750 mg every 8 hours. No new safety findings were identified. As a result of the assessement of study C211, the CHMP was of the opinion that Incivo 1125 mg can be administered orally twice daily. The results of the study are applicable to all patients for whom telaprevir is indicated.
II/0008/G	This was an application for a group of variations.	25/04/2013	27/05/2013	SmPC and PL	The assessment of these studies demonstrated that Incivo

	Gouping of 6 variations to updates the sections 4.5 and 5.2 of the SmPC with new information on the involvement of aldo-ketoreductases in the metabolism of telaprevir based on the data from the study DMPK-DM-047, the in vitro CYP induction potential of telaprevir based on the data from the study H160 and study B050860, the UGT inhibition potential of telaprevir based on the data from the study FK10205, the inhibition potential of telaprevir on alcohol dehydrogenase based on the data from the study FK10206, the interaction of telaprevir with organic anion transporter polypeptides (OATPs) and the in vitro inhibition potential of telaprevir on OATPs, OAT1 and OCT2 based on the data from the study FK10183. Data from study H160 was submitted as a follow up to MEA010.1. The PL is updated in accordance. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-				is a strong, time dependent inhibitor of CYP3A4 and also markedly inhibits P-gp. The time dependency indicates that inhibition of CYP3A4 may be intensified during the first 2 weeks of treatment. After ending treatment, approximately one week may be needed for the inhibition to completely disappear. Other enzymes may also be involved in the metabolism e.g aldo ketoreductases and other proteolytic enzymes. No relevant inhibition by Incivo of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6, and CYP2E1 isozymes was observed in vitro. Based on the results of drug drug interaction clinical studies (e.g., escitalopram, zolpidem, ethinylestradiol), induction of metabolic enzymes by telaprevir cannot be excluded. In vitro studies demonstrated that Incivo is an inhibitor of OATP1B1 and OATP2B1. Incivo inhibits organic anion transporter polypeptides (OATPs) OATP1B1 and OATP2B1. Concomitant administration of Incivo and drugs transported by these transporters such as fluvastatin, pravastatin, rosuvastatin, pitavastatin, bosentan and repaglinide should be undertaken with caution. Simvastatin is contraindicated due to the predicted marked increase in exposure caused by multiple mechanisms. In vitro studies demonstrated that Incivo is not an inhibitor of UGT1A9 or UGT2B7. In vitro studies with recombinant UGT1A3 suggested that telaprevir may inhibit this enzyme. The clinical relevance of this is uncertain as administration of Incivo with a single dose of buprenorphine, a partial UGT1A3 substrate, to healthy adult subjects did not result in increases in buprenorphine exposures. No relevant inhibition by Incivo of alcohol dehydrogenase was observed in vitro. However, sufficiently high concentrations were not tested for intestinal inhibition to be excluded.

	clinical, clinical or pharmacovigilance data C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				
II/0013	Update of sections 4.4 and 4.8 of the SmPC with information on reported Toxic Epidermal Necrolysis (TEN). The recommendations for the monitoring and management of rash have been updated in section 4.4. Update of section 4.8 of the SmPC with information on reported erythema multiforme (EM) cases. The PL is updated accordingly. Spelling errors were corrected in Section 4.2 of the SmPC and in Annex II. In addition, proposal to issue a Direct Healthcare Professional Communication letter to draw the attention of the treating physicians to this new ADR. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	21/03/2013	22/04/2013	SmPC, Annex II and PL	Two post marketing reports of toxic epidermal necrolysis (TEN), one with a fatal outcome, were reported from the Drug Use-Results Surveillance Program in Japan. The issue of the management of telaprevir, as well as peginterferon and ribavirin, in case of telaprevir-associated rash is extensively covered in the current product information. It seems that these principles were not followed in the management of the TEN cases. This stresses the importance of adhering to the recommendations for the monitoring and management of rash given in the product information, including immediate discontinuation of Incivo if severe rash develops. In addition, emerging data suggest that co-treatment with peginterferon and ribavirin can contribute to rash; these medications may also need to be stopped in case of Incivo-related rash. Erythema multiforme (EM) cases were also reported with a rare frequency. A Dear Health Care Provider letter has been circulated to inform prescribers of these events and advise them to remind their patients to contact their doctor immediately if they develop a rash or have a rash that gets worse.
II/0009	Update of sections 4.4 and 4.5 of the SmPC with information on the CYP3A4 inhibitory effect of telaprevir and use with fentanyl and alfentanil. The PL is updated accordingly. In addition, the MAH took the opportunity to update the Annex II in accordance to the latest QRD template.	21/02/2013	22/04/2013	SmPC, Annex II and PL	Telaprevir is a strong inhibitor of CYP3A4. Careful monitoring of therapeutic and adverse effects (including respiratory depression) is recommended when telaprevir is co-administered with alfentanil or fentanyl, including oral, buccal, nasal and extended-release transdermal or transmucosal preparations of fentanyl, especially at

	C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				initiation of treatment. Dosage adjustment of fentanyl or alfentanil may be necessary. The most marked effects are expected on oral, nasal and buccal/sublingual fentanyl formulations.
IB/0012/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.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	25/01/2013	n/a		
II/0010	Update of sections 4.4, 4.8 and 5.1 of the SmPC with the outcomes of the SVR12 data of the ongoing Phase 2a Study 110 in HCV-1/HIV-1 coinfected subjects. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	18/10/2012	19/11/2012	SmPC	The MAH updated sections 4.4, 4.8 and 5.1 of the SmPC with the results of an interim analysis of an ongoing pilot study in hepatitis C virus (HCV)/human immunodeficiency virus (HIV)-coinfected patients. HCV/HIV-coinfected patients are an important subgroup of HCV patients that have more rapid disease progression and lower response to peginterferon/ribavirin therapy. The presented data showed that, as in HCV-monoinfected patients, telaprevir also adds to the efficacy in coinfected patients, as measured by sustained virological response (i.e. HCV RNA <25 IU/mL) 12 weeks after the last dose of study drug (SVR12). The preliminary data also indicates that the safety profile of telaprevir in HCV/HIV-coinfected patients is similar to that seen in monoinfected patients.
II/0006	Update of section 4.5 of the SmPC with the results of	20/09/2012	25/10/2012	SmPC and PL	The MAH has performed an interaction study in two parts,

	a drug-drug interaction study (TMC125IFD1001) with telaprevir, rilpivirine and etravirine. This study is part of the commitments included in the Risk Management Plan. In addition, a minor correction is made to section 6.5 of the SmPC and sections 5 & 6 of PL (dessicant information: one or two pouches can be present in a bottle) to align it with the information in Module 3. The PL was further updated with the contact information for the local representative in Cyprus. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				which adequately addresses 1) the effect of telaprevir on etravirine, and vice versa, and 2) the effect of telaprevir on rilpivirine, and vice versa. The effect on the AUC, Cmax and Cmin of the respective compound is summarized in the updated Incivo SmPC section 4.5, Table 2, along with the recommendation that no dose adjustment is required if the drugs are co-administered. The conclusions drawn by the MAH are, in general, agreed upon. This variation does not affect the benefit/risk balance of Incivo.
IAIN/0011	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	23/08/2012	n/a		
IB/0007/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.3.a - Change in batch size (including batch size ranges) of AS or intermediate - Up to 10-fold increase compared to the currently approved batch size	19/07/2012	n/a		
II/0004	Update of section 4.5 of the SmPC with the results of a drug-drug interaction study with telaprevir and buprenorphine. C.I.4 - Variations related to significant modifications	16/02/2012	19/03/2012	SmPC	The final results of a drug-drug interaction study of telaprevir with buprenorphine have been submitted. Results showed that buprenorphine exposure was not affected during coadministration with telaprevir. Telaprevir exposure during coadministration with buprenorphine/naloxone was

	of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				comparable to historical telaprevir exposure when telaprevir was administered alone. Therefore, telaprevir and buprenorphine can be coadministered without dose modifications.
II/0003	Update of section 4.5 of the SmPC with the results of a drug-drug interaction study with telaprevir and raltegravir. In addition since a definitive ATC code has been assigned to Telaprevir by the WHO this code has been added to the product information. The MAH also took the opportunity to update the list of local representatives in the PL. Furthermore, the PI is being brought in line with the latest QRD template version. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	16/02/2012	19/03/2012	SmPC, Annex II, Labelling and PL	The final pharmacokinetics and safety data of a drug-drug interaction study of telaprevir with raltegravir have been submitted. Results showed that telaprevir exposure was not affected by concomitant administration of raltegravir. Raltegravir exposure was increased by 31% during coadministration with telaprevir. Due to the safety profile of raltegravir, this increase is not considered to be clinically relevant. Therefore telaprevir and raltegravir can be coadministered without dose modifications.
IB/0005	B.II.b.3.z - Change in the manufacturing process of the finished product - Other variation	20/02/2012	n/a		
N/0002	The MAH took this opportunity to update the contact details of the local representatives in Cyprus, Romania, Spain and Slovakia. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	12/12/2011	19/03/2012	PL	The MAH took this opportunity to update the contact details of the local representatives in Cyprus, Romania, Spain and Slovakia.
IB/0001	B.II.e.5.a.2 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change outside the range of the currently approved pack sizes	13/10/2011	13/10/2011	SmPC, Labelling and PL	
