EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Victrelis

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/0042	Update of section 4.4 of the SmPC to add a warning regarding HBV reactivation observed in patients with HCV/HBV co-infection treated with some direct-acting antivirals not given in combination with peginterferon alfa and ribavirin. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to implement minor editorial updates in the Product Information.	29/06/2017		SmPC and PL	Even though no cases of HBV reactivation have been reported in post-marketing in patients receiving boceprevir in combination with peginterferon alfa and ribavirin, a theoretical risk cannot be excluded since boceprevir is a direct antiviral agent of first generation. In line with the PRAC conclusions on HCV Direct Antiviral Agent article 20 referral of December 2016, the CHMP agreed to add in section 4.4 of the SmPC a warning regarding HBV

[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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	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				reactivation.
II/0041	In line with the Latuda Product Information and following data obtained from the MAH continuous safety monitoring, update of sections 4.3 and 4.5 of the SmPC in order to add lurasidone in the list of contraindicated medications. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to implement QRD template version 10, including implementation of the 2D barcode in the PI. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	21/04/2017		SmPC, Labelling and PL	
IB/0040	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	01/03/2017		SmPC and PL	
II/0039	Submission of the final report for the cat 3 Observational Post-Authorization Safety Study of Victrelis among Chronic Hepatitis C patients (P08518). The updated RMP version 10.1 is agreed. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	10/11/2016	n/a		

PSUSA/9081/201511	Periodic Safety Update EU Single assessment - boceprevir	09/06/2016	n/a		PRAC Recommendation - maintenance
R/0036	Renewal of the marketing authorisation.	17/12/2015	18/02/2016	SmPC, Annex II, Labelling and PL	
II/0037	C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required	14/01/2016	06/02/2017	SmPC, Annex II and PL	
II/0035	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	24/09/2015	n/a		
PSUSA/9081/201411	Periodic Safety Update EU Single assessment - boceprevir	11/06/2015	n/a		PRAC Recommendation - maintenance
II/0033	Submission of the final report of HCP Educational Material Impact study for Victrelis compiling the results of all the EU countries where the product is marketed (France, Germany, Spain, United Kingdom and Italy). C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	26/03/2015	n/a		
PSUV/0031	Periodic Safety Update	18/12/2014	19/02/2015	SmPC and PL	Please refer to Victrelis PSUV 0031 EPAR:

					Scientific conclusions and grounds recommending the variation to the terms of the marketing authorisation
II/0032	Update of section 4.2 of the SmPC, upon request by the CHMP following the assessment of LEG 032, in order to highlight the negative predictive value of TW4 on treatment response. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	22/01/2015	18/02/2016	SmPC	In poorly interferon responsive patients (defined as < 1 log10 decline in HCV RNA at TW 4) the use of triple therapy should be considered on a case by case basis, as the likelihood of achieving sustained virologic response (SVR) with triple therapy is lower in these patients.
II/0030	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		
PSUV/0028	Periodic Safety Update	26/06/2014	22/08/2014	SmPC and PL	Please refer to the Victrelis PSUV-28 EPAR: Scientific conclusions and grounds recommending the variation to the terms of the marketing authorisation
II/0029	C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required	24/07/2014	n/a		
II/0027	Update of section 4.2 of the SmPC with an additional stopping rule for treatment week 8 in order to discontinue treatment early in patients who are unlikely to attain SVR. The additional stopping rule is based on analysis of pooled efficacy data from five previously submitted Phase 3 studies.	20/02/2014	21/03/2014	SmPC	Based on analysis of pooled efficacy data from Phase 3 studies (P05101, P05685, and P05514 in treatment-experienced patients; P05216 and P06086 in treatment-naïve patients) the proposed TW8 futility rule of HCV-RNA ≥1000 IU/mL was confirmed as the most appropriate among the potential stopping rules identified by the MAH. Post hoc analysis of the application of this additional rule

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				did not considerably impact the overall SVR rate in treatment-naïve or treatment-experienced patients (<1% in both groups) while it allowed for an earlier discontinuation of BOC/PR in a significant number of patients unlikely to achieve SVR, therefore reducing the risk of emerging resistance and toxicity.
PSUV/0024	Periodic Safety Update	18/12/2013	17/02/2014	SmPC and PL	Please refer to: H-2332-PSUV-24 "Scientific conclusions and grounds recommending the variation to the terms of the marketing authorisation."
IB/0026	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	18/12/2013	22/01/2014	SmPC and PL	Section 4.3 and 4.5 of the SmPC are updated to include a contra-indication for the use of quetiapine. Section 2 of the PL is updated accordingly.
II/0022	Update of the timeline for completion of the Annex II obligation to conduct a phase 3, safety and efficacy study of boceprevir/peginterferon alfa-2a/ribavirin in chronic HCV genotype 1 IL28B CC subjects. C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required	21/11/2013	17/02/2014	Annex II	As a condition of the Victrelis marketing authorisation study P07755 was requested by the CHMP to determine whether boceprevir has added value over therapy with peginterferon alfa plus ribavirin alone. The expected date for availability of the final study report for P07755 is delayed beyond the agreed submission date of May 2014 until October 2015 and changes are proposed to be made to the study protocol.
IG/0366	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	08/11/2013	n/a		
IA/0023	B.I.a.2.a - Changes in the manufacturing process of	28/10/2013	n/a		

	the AS - Minor change in the manufacturing process of the AS				
II/0014	Update of section 5.1 of the SmPC with information on the longevity of resistance-associated variants (RAVs) in boceprevir-treated patients who did not achieve sustained virologic response (SVR), and on the durability of viral suppression in boceprevir-treated patients who achieved SVR, based on long-term follow-up study P05063 (assessed in MEA019, 019.1 and 019.2). In addition, the MAH took this opportunity to include minor editorial changes in the SmPC. C.I.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under Article 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH	24/10/2013	17/02/2014	SmPC	Long-term follow up of patients who did not achieve sustained virologic response (SVR) in the boceprevir phase 2 and 3 clinical trials demonstrated that Hepatitis C Virus resistance-associated variants (RAVs) are replaced in the viral population by wild type virus at rates that likely reflect clinical fitness of the resistant variants. Within 3 years post-therapy, 73% (228/314) of subjects no longer had any RAVs detected by population sequencing (detection limit ~20-25% of the total virus population), with a median time for all RAVs to become undetectable of 1.11 years. However, no data are available regarding the efficacy of boceprevir among patients who previously failed treatment with a boceprevir-containing regimen, and the long-term clinical impact of the emergence or persistence of boceprevir RAVs is unknown. The long-term follow-up data also confirmed the durability of viral suppression, with >99% of patients maintaining their SVR through the available follow-up period (median duration of 3.4 years).
II/0021	Update of section 5.1 of the SmPC with final data on boceprevir treatment in adults with chronic hepatitis C, who were prior treatment failures to peginterferon and ribavirin therapy (study P05514). Study P05514 is a required activity of the Pharmacovigilance Plan of the Victrelis RMP. In addition the MAH corrected some spelling mistakes in the PL.	19/09/2013	17/02/2014	SmPC and PL	Study P05514 (PROVIDE) was a single-arm, open label, multicentre, rollover study that offered boceprevir therapy in combination with peginterferon alfa-2b and ribavirin ("tritherapy") to subjects with chronic hepatitis C genotype 1 infection who were in the peginterferon alfa/ribavirin ("bitherapy") control arms of prior studies of boceprevir and failed to achieve sustained virologic response (SVR). The results of this study confirmed that patients who failed

	C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				to achieve SVR with bimeotry benefit significantly from boceprevir tritherapy. SVR rates in patients who received at least one dose of boceprevir were 41% in prior null responders, 67% in prior partial responders and 96% in prior relapsers. The safety profile of tritherapy was similar to the one reported in previous boceprevir studies.
II/0019	Update of section 4.4 of the SmPC with information on anaemia and neutropenia, resulting from a post hoc analysis of clinical trial data on anaemia and clinical observations on neutropenia and its monitoring by blood counts. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	19/09/2013	17/02/2014	SmPC	Based on a post hoc analysis of clinical trial data on anaemia and clinical observations on neutropenia the MAH proposed to revise the recommendations regarding monitoring of these two adverse reactions in section 4.4 of the SmPC. For anaemia, since the observed time-to-onset of anaemia from initiation of treatment ranged from of 15-337 days with a median of 71 days, the MAH proposed two additional complete blood counts, at treatment week 2 and 12. For neutropenia, in clinical trials a rapid decline in neutrophil count was observed as early as treatment week 2, with neutrophil counts stabilising after 8 to 12 weeks of therapy. The MAH thus proposed that neutropenia should be monitored at the same time as anaemia, i.e. pre-treatment, at treatment weeks 2, 4, 8 and 12, and at other time points as clinically appropriate, by complete blood counts with white blood cell differential counts. These recommendations for reinforced monitoring were supported by the CHMP.
PSUV/0020	Periodic Safety Update	27/06/2013	03/09/2013	SmPC and PL	Please refer to: H-2332-PSUV-20 “Scientific conclusions and grounds recommending the variation to the terms of the marketing authorisation.”
II/0017/G	This was an application for a group of variations.	25/07/2013	17/02/2014	SmPC and PL	The MAH has performed three clinical studies in healthy volunteers to investigate potential drug-drug interactions

	Update of section 4.5 of the SmPC with information on drug-drug interactions with raltegravir (study P102), rilpivirine (study P103) and sirolimus (study P106). The PL is updated accordingly. Furthermore, the MAH took this opportunity to include a minor editorial change in section 4.4 and a minor correction in section 4.5 of 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 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				between boceprevir and raltegravir, rilpivirine or sirolimus. Based on the results of these studies, the CHMP concluded that no dose adjustment was required when raltegravir or rilpivirine are co-administered with boceprevir. However, since the clinical relevance of the observed decrease in boceprevir C8hr during co-administration with raltegravir has not been established, increased clinical/laboratory monitoring are warranted when boceprevir and raltegravir are co-administered. For sirolimus, data showed a marked increase in sirolimus exposure following concomitant administration of multiple doses of boceprevir. Therefore co-administration of boceprevir with sirolimus requires significant dose reduction and prolongation of the dosing interval for sirolimus, with close monitoring of sirolimus blood concentrations and frequent assessments of renal function and sirolimus-related side effects.
II/0015	Update of sections 4.4, 4.8 and 5.1 of the SmPC with information on boceprevir treatment in adults with HCV/HIV co-infection from study P05411. In addition, the MAH took the opportunity to update the list of local representatives in the PL to include contact details for the representative of Croatia. Furthermore, the MAH implemented minor editorial changes in section 5.1, and the PI is being brought in line with the latest QRD template version 9.0. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	27/06/2013	03/09/2013	SmPC, Annex II and PL	Study P05411 was a Phase IIb, randomised, double-blind, multicentre, placebo-controlled clinical trial evaluating the efficacy and safety of boceprevir in combination with peginterferon alfa and ribavirin (PR) in adult patients coinfected with Human immunodeficiency virus (HIV) and previously untreated chronic Hepatitis C virus (HCV) genotype 1. As in HCV-monoinfected patients, addition of boceprevir to PR significantly increased the sustained virologic response (SVR) rate in HCV/HIV-coinfected patients. The SVR24 rate was 62.5%, confirming that with a more potent tritherapy regimen HCV/HIV-coinfected patients can achieve a comparable response rate to HCV-monoinfected patients. Of note, as expected from the recently identified drug-drug interaction between

					boceprevir and boosted HIV protease inhibitors (PIs), boceprevir blood levels were reduced in study P05411; nevertheless there was no obvious signal of loss of HIV virological control or lower SVR rate in patients receiving boosted PIs. The safety profile of boceprevir/PR tritherapy in HCV/HIV-coinfected patients was similar to that observed in HCV-monoinfected patients.
IA/0016/G	This was an application for a group of variations. B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS A.5.b - Administrative change - Change in the name and/or address of a manufacturer of the finished product, including quality control sites (excluding manufacturer for batch release)	26/03/2013	n/a		
II/0013	Update of section 4.4 of the SmPC with information on hypersensitivity reactions, and addition of the adverse events angioedema and drug rash with eosinophilia and systemic symptoms (DRESS) to section 4.8 of the SmPC. These updates were based on the identification of new post-marketing signals. The Package Leaflet was updated accordingly. The MAH also took the opportunity to implement minor editorial changes in sections 3 and 4 of the Package Leaflet. 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	03/09/2013	SmPC and PL	Based on a cumulative search of the MAH's adverse events database the MAH proposed to include several adverse reactions in the product information. Following an analysis of the submitted cases the CHMP endorsed the addition to section 4.8 of the SmPC of angioedema and drug rash with eosinophilia and systemic symptoms (DRESS) under the frequency category Not known (frequency cannot be estimated from the available data), noting that cases of DRESS were reported less frequently and were less severe with boceprevir than what has been observed so far with telaprevir. The CHMP also supported the addition of a warning for hypersensitivity in section 4.4. The MAH's other claims (Stevens-Johnson syndrome, rash exfoliative, dermatitis exfoliative, toxic skin eruption and toxicoderma)

					were based on isolated, mostly poorly documented cases, in which the causality of boceprevir cannot be fully established. The addition of these adverse events to section 4.8 was thus not endorsed by the CHMP at this moment in time, but the MAH was requested to continue to closely monitor for all cases of serious cutaneous reactions. Of note, rash exfoliative, dermatitis exfoliative, toxic skin eruption and toxicoderma are already covered under more general terms of rash and dermatitis under the frequency category common.
II/0012	Update of section 4.5 of the SmPC with information on the drug-drug interaction with atorvastatin. In addition, the MAH took the opportunity to update the list of local representatives for Czech Republic and Slovakia in the PL. 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	03/09/2013	SmPC and PL	Based on a re-evaluation of a drug-drug interaction study with atorvastatin (P08124) in the context of the atorvastatin prescribing information, the MAH proposed to limit the maximum daily dose of atorvastatin when co-administered with boceprevir. Since boceprevir increases exposure to atorvastatin by >2-fold, the maximum daily dose of atorvastatin during co-administration was limited to 20 mg, to ensure the resulting exposure during co-administration does not exceed the exposure following the maximum recommended daily atorvastatin dose in the absence of boceprevir (80 mg).
II/0011	Update of section 4.5 of the SmPC with information on drug-drug interactions with oral contraceptives containing ethinyl estradiol and norethindrone. The Package Leaflet is updated accordingly. 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	03/09/2013	SmPC and PL	The drug-drug interaction study P08335 was performed to evaluate the effect of boceprevir on a combined oral contraceptive (COC) containing 35 µg ethinyl estradiol (EE) combined with 1 mg norethindrone (NET). Following co-administration with boceprevir, no clinically relevant changes were observed in NET pharmacokinetic parameters, but plasma exposure and Cmax for EE decreased significantly, by ~26% and 21% respectively. Of note, surrogate markers for the pharmacodynamic response to COC (levels of serum progesterone, luteinising

					hormone, follicle-stimulating hormone and sex hormone-binding globulin) were within a range considered relevant for contraceptive efficacy. The CHMP therefore concluded that the decrease in EE exposure is not expected to be clinically relevant, and that coadministration with boceprevir is unlikely to alter the effectiveness of the tested COC. However, in view of the reduced exposure to EE the CHMP recommended clinical monitoring for signs of oestrogen deficiency in patients using oestrogens as hormone replacement therapy.
II/0008/G	This was an application for a group of variations. Grouping of six variations to update section 4.5 of the SmPC with new information on the drug-drug interaction between boceprevir and methadone, buprenorphine/naloxone, omeprazole, etravirine, raltegravir, digoxin and prednisone (studies P08123, P08502, P08508, P08371, P08431 and P08514). The PL was updated accordingly. In addition the MAH took this opportunity to bring Annex II in line with the QRD template version 8.3, and to amend in the PL the contact details of the representative for Greece. 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	21/02/2013	03/09/2013	SmPC, Annex II and PL	Patients with chronic hepatitis C (CHC) often receive multiple medications to treat other conditions which frequently coexist in these patients (such as HIV infection, opioid addiction etc); therefore it is important to understand drug interactions with drugs that may be co-administered in this patient population. The MAH has performed six studies to investigate potential drug-drug interactions between boceprevir and methadone, buprenorphine/naloxone, omeprazole, etravirine, raltegravir, digoxin and prednisone. All studies were adequately performed and the effect of boceprevir on the pharmacokinetic parameters of the respective compounds (and vice versa if investigated) was included in section 4.5 of the SmPC. Based on these results, the CHMP concluded that no dose adjustment was required when any of the above-listed compounds are coadministered with Victrelis. However, the CHMP also recommended that these patients should be monitored appropriately.

	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				
II/0006	In fulfilment of the obligation "The MAH should provide results of study P06086 to further substantiate the impact of the management of anaemia on the efficacy and safety of therapy with Victrelis. The results of the Study P06086 will be submitted by April 2012" sections 4.4 and 5.1 of the SmPC have been updated based on the results from this study. Annex II was updated accordingly and was also brought in line with the latest QRD template. Minor editorial changes to section 4.8 of the SmPC were also introduced. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	17/01/2013	03/09/2013	SmPC and Annex II	Study P06086 was designed to investigate the efficacy and safety of ribavirin dose reduction versus erythropoietin (EPO) as primary anaemia management strategies in adult subjects with previously untreated chronic hepatitis C genotype 1 infection who become anaemic (serum haemoglobin ≤10 g/dl) during tritherapy with boceprevir plus peginterferon alfa and ribavirin. Both anaemia management strategies resulted in comparable efficacy with sustained virologic response (SVR) 24 rates of 71.5% in Arm 1 (ribavirin dose reduction) and 70.9% in Arm 2 (EPO use). The safety profile was comparable between Arm 1 and 2 and was consistent with the known safety profile of tritherapy. However, the use of EPO was associated with an increased risk of thromboembolic events. These data dispel the concerns towards a negative impact of ribavirin dose reduction on the treatment response. Given the safety issues associated with EPO use, the SmPC was amended to clarify that ribavirin dose reduction is the preferred strategy for managing treatment-emergent

					anaemia.
II/0007	Following the availability of the interim analysis' results of the study P05514, deletion of a warning in section 4.4 and update of section 5.1 of the SmPC with new information on the treatment in adults with chronic hepatitis C who were prior treatment failures to peginterferon and ribavirin therapy (null responders). A correction was made in Section 5.2 of the SmPC. The PL was updated accordingly. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	15/11/2012	03/09/2013	SmPC and PL	Study PROVIDE (P05514) is an on-going open-label, single-arm study of Victrelis in combination with peginterferon alfa-2b and ribavirin in adult subjects with chronic hepatitis C (HCV) genotype 1 infection who did not achieve Sustained Virological Response (SVR). The interim SVR analysis is based on 85% of subjects enrolled. Most of the subjects who were null responders (50/52) are included in the interim analysis. The SVR rate was 38% (19/50) in subjects who were null responders and received at least one dose of any study medication. The CHMP concluded that the benefit of BOC in combination with peginterferon alfa and ribavirin in treating prior null responders has been demonstrated in study P05514 (PROVIDE) and agreed to the deletion of the warning in section 4.4 and the update of section 5.1 of the SmPC with new information from this study.
IG/0184	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	21/08/2012	n/a		
IA/0009/G	This was an application for a group of variations. B.II.e.2.b - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Addition of a new specification parameter to the specification with its corresponding test method B.II.e.2.c - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete	21/08/2012	n/a		

	parameter)				
II/0005	Update of section 4.3 of the SmPC with a new contraindication with simvastatin and lovastatin and section 4.5 of the SmPC with information on interactions with cyclosporine, tacrolimus, sirolimus, escitalopram, atorvastatin and pravastatin. The PL is updated in accordance. Change to section 4.6 of the SmPC with new information on contraceptive measures and to section 5.1 of the SmPC with updated information on resistance were also introduced. Changes were also made to the SmPC, Annex II, Labelling and PL to bring it in line with the current QRD template. In addition, the list of local representatives in the PL has been revised to amend contact details for the representatives of Ireland, Iceland, Italy, Hungary, Malta, Netherlands and Portugal. In addition, translation mistakes were corrected in the product information for all EU languages. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	21/06/2012	31/07/2012	SmPC, Annex II, Labelling and PL	Following the completion of a Drug-Drug Interaction study (P08124) characterizing the pharmacokinetic interactions between Victrelis and cyclosporine, tacrolimus, escitalopram, atorvastatin and pravastatin, section 4.5 of the SmPC has been updated with new information on these interactions. Victrelis pharmcokinetics were not significantly altered by cyclosporine or tacrolimus. The concomitant administration of Victrelis and cyclosporine led to significant changes in cyclosporine pharmacokinetics (Cmax increased by 101% and AUC by 168%). Cyclosporine half-life was increased from 11 to 16h and tacrolimus half-life from 37 to 62h. The AUC and Cmax of tacrolimus increased in an even more substantial manner (Cmax increases by 890% and AUC by 1610%) when combined with Victrelis. The results obtained with these immunosuppressants were extrapolated to sirolimus. Therefore, similar recommendations for all compounds are made in the SmPC: dose adjustment with close monitoring of concentration, renal function and side effects to all immunosuppressants. Victrelis pharmcokinetics were not significantly altered by escitalopram. On the other hand, escitalopram exposure and Cmax were reduced by 21% and 19% respectively, when coadministered with Victrelis. No dose adjustment of escitalopram when given together with Victrelis is recommended; however, doses of escitalopram may need to be adjusted based on clinical effect. Victrelis significantly increased the exposure (AUC by 130% and Cmax by 166%) of atorvastatin. In line with these findings, dose reduction of atorvastatin should be

					considered when co-administrated with Victrelis. Additional clinical monitoring is recommended when daily doses of atorvastatin exceed 40 mg. The exposure of pravastatin is increased when co-administered with Victrelis (AUC by 63% and Cmax by 49%). Pravastatin did not affect the exposure of Victrelis. In line with these findings, treatment with pravastatin can be initiated at the recommended dose when co-administered with Victrelis. However, close clinical monitoring is warranted. Moreover, a new contraindication for co-administration of Victrelis with simvastatin and lovastatin has been introduced.
II/0004	Update of sections 4.4 and 4.5 of the SmPC with information on interaction with boosted protease inhibitors. Annex II.B and the PL were proposed to be 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	16/02/2012	21/03/2012	SmPC, Annex II and PL	A drug interaction study in healthy volunteers carried out by the marketing authorisation holder of Victrelis, found that blood levels of all three HIV medicines were markedly lower than expected when given with Victrelis. It also found that blood levels of Victrelis were markedly lower than expected when given with ritonavir-boosted darunavir or lopinavir, although this effect was not seen with ritonavir-boosted atazanavir. The Agency's Committee for Medicinal Products for Human Use (CHMP) concluded that the lower blood levels seen in the drug interaction study could mean that the medicines are less effective when given together to patients who are co-infected with HCV and HIV. However, the Committee acknowledged that data from ongoing clinical studies in co-infected patients are needed to assess the clinical impact of these drug-interaction findings on these patients. Studies on the efficacy and safety of Victrelis when used in patients co-infected with HIV and HCV are ongoing.

					While data from these studies are awaited, the CHMP has recommended updating the product information to inform prescribers and patients of the findings as a precautionary measure. Co-administration of Victrelis with ritonavir-boosted darunavir or lopinavir in HIV and HCV co-infected patients is not recommended. Co-administration of Victrelis with ritonavir-boosted atazanavir may be considered on a case-by-case basis in patients with suppressed HIV viral loads and with an HIV strain without any suspected resistance to the HIV regimen. Increased clinical and laboratory monitoring is warranted.
IAIN/0003/G	This was an application for a group of variations. B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes A.6 - Administrative change - Change in ATC Code/ATC Vet Code	02/02/2012	21/03/2012	SmPC, Labelling and PL	
IG/0117/G	This was an application for a group of variations. C.I.9.c - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the back-up procedure of the QPPV C.I.9.g - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the site undertaking pharmacovigilance activities C.I.9.a - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the QPPV	18/11/2011	21/03/2012	Annex II	

	C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system				
N/0001	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	24/08/2011	n/a	PL	