Isentress

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/10373 /201709	Periodic Safety Update EU Single assessment - raltegravir	12/04/2018	n/a		PRAC Recommendation - maintenance
II/0064/G	This was an application for a group of variations. Extension of indication to include treatment of HIV-1 exposed neonates (under the age of 4 weeks) based on safety and PK data from one pivotal Phase 1 study, IMPAACT P1110 (Protocol 080), in a total of	22/02/2018	23/03/2018	SmPC, Labelling and PL	Please refer to Scientific Discussion Isentress H-0860-II-64-G-AR

[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).

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5520
Send a question via our website www.ema.europa.eu/contact

	42 HIV-1 exposed full-term infants (defined as ≥37 weeks gestational age and ≥2000 g), who received either 2 single doses of oral suspension, within 48 hours of birth and Day 7-10 of age (Cohort I), or a multiple-dose regimen of raltegravir over the first 6 weeks of age (Cohort II). As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC have been updated and the Package Leaflet has been updated accordingly. Further, the suspension volume has been updated from 5 mL to 10 mL for a final suspension concentration of 10 mg/mL to facilitate accurate measurement of the smaller doses required for neonates. As a consequence, the 5 mL syringe previously supplied in the presentation for granules for oral suspension is replaced with 3 new oral dosing syringes of various sizes (1 mL, 3 mL, and 10 mL), from a different (new) supplier. As a consequence, sections 6.5 and 6.6 of the SmPC have been updated and the labelling and instructions for use in the Package Leaflet have been updated accordingly. An updated RMP version 14.0 was agreed during the procedure. B.IV.1.a.1 - Change of a measuring or administration device - Addition or replacement of a device which is not an integrated part of the primary packaging - Device with CE marking C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				

II/0069	Update of section 4.8 of the SmPC of all strengths and of section 5.1 of the 600 mg strength SmPC based on the final results (i.e. through 96 weeks) of study PN292 (ONCEMRK), the pivotal Phase 3 study evaluating the safety and efficacy of raltegravir 1200 mg QD (2 x 600 mg tablets) versus raltegravir 400 mg BID, each in combination with emtricitabine/tenofovir disoproxil fumarate in treatment-naïve HIV-1 infected adult subjects. In addition, the MAH took the opportunity to implement minor editorial changes in the SmPC. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	08/02/2018	23/03/2018	SmPC	In randomised clinical trials raltegravir 400 mg twice daily was administered in combination with fixed or optimised background treatment regimens to treatment naïve (N=547) and treatment-experienced (N=462) adults for up to 96 weeks. A further 531 treatment naïve adults have received raltegravir 1,200 mg once daily with emtricitabine and tenofovir disoproxil fumarate for up to 96 weeks. The most frequently reported adverse reactions during treatment were headache, nausea and abdominal pain. The most frequently reported serious adverse reaction was immune reconstitution syndrome and rash. The rates of discontinuation of raltegravir due to adverse reactions were 5% or less in clinical trials. Rhabdomyolysis was an uncommonly reported serious adverse reaction in post-marketing use of raltegravir 400 mg twice daily. At Week 96, the proportion of patients achieving HIV RNA < 40 copies/ml was 433/531(81.5 %) in the group receiving raltegravir 1,200 mg once daily and 213/266 (80.1 %) in the group receiving raltegravir 400 mg twice daily. The treatment difference (raltegravir 1,200 mg once daily-raltegravir 400 mg twice daily) was 1.5 % with an associated 95 % CI of (-4.4, 7.3). Week 48 and Week 96 outcomes from ONCEMRK are provided in detail in section 5.1 of the updated SmPC.
IB/0071/G	This was an application for a group of variations. B.II.b.1.e - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch-	28/11/2017	n/a		

	release, batch control, primary and secondary packaging, for non-sterile medicinal products 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 B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process				
PSUSA/10373 /201703	Periodic Safety Update EU Single assessment - raltegravir	26/10/2017	n/a		PRAC Recommendation - maintenance
IB/0070/G	This was an application for a group of variations. B.II.b.1.e - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non-sterile medicinal products 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 B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.5.a - Change to in-process tests or limits applied during the manufacture of the finished	13/10/2017	n/a		

	product - Tightening of in-process limits				
IB/0068	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	13/10/2017	23/03/2018	SmPC, Labelling and PL	
IA/0067	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	21/09/2017	n/a		
IA/0066	A.7 - Administrative change - Deletion of manufacturing sites	10/08/2017	n/a		
X/0059	Annex I_2.(c) Change or addition of a new strength/potency	18/05/2017	13/07/2017	SmPC, Labelling and PL	
PSUSA/10373 /201609	Periodic Safety Update EU Single assessment - raltegravir	06/04/2017	n/a		PRAC Recommendation - maintenance
II/0061	Update of section 4.2 of the SmPC of Isentress 100 mg granules for oral suspension, upon request by PRAC following the assessment of the latest PSUR for raltegravir (EMEA/H/C/PSUSA/00010373/201509), to add information relating to the maximum dose of Isentress being 100 mg twice a day, and the fact that each single-use packet for oral suspension is suspended in 5mL of water giving a final concentration of 20mg/ml. In addition, the MAH took the opportunity to implement minor editorial changes	29/09/2016	14/11/2016	SmPC, Annex II, Labelling and PL	N/A

	in the annexes, to update the contact details of the local representative in Luxembourg in the Package Leaflet and to align the annexes with the latest QRD templates (versions 9.1 and 10). C.I.3.b - 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 - Change(s) with new additional data submitted by the MAH				
PSUSA/10373 /201603	Periodic Safety Update EU Single assessment - raltegravir	27/10/2016	n/a		PRAC Recommendation - maintenance
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.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites	15/09/2016	n/a		
PSUSA/10373 /201509	Periodic Safety Update EU Single assessment - raltegravir	14/04/2016	n/a		PRAC Recommendation - maintenance

IA/0058	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	13/04/2016	n/a		
IB/0055	B.II.b.5.b - Change to in-process tests or limits applied during the manufacture of the finished product - Addition of a new test(s) and limits	14/10/2015	n/a		
PSUSA/2604/ 201503	Periodic Safety Update EU Single assessment - raltegravir	08/10/2015	n/a		PRAC Recommendation - maintenance
II/0052	Submission of 5th and Final Report of the five-year EuroSIDA post-authorisation observational study. 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		The MAH was requested to conduct an observational study to monitor the general safety of raltegravir and perform surveillance for malignancies, effects on the liver, lipodystrophy and all-cause mortality in light of the relatively limited safety information from the pivotal trials (MEA). This is the 5th and final report for this PAM.
IB/0056/G	This was an application for a group of variations. B.II.b.1.e - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non-sterile medicinal products 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	11/09/2015	n/a		

	B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process				
IA/0053/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites	10/04/2015	n/a		
N/0051	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	10/02/2015	19/11/2015	Labelling	
II/0050	Update of section 4.5 of the SmPC further to the results of drug-drug interaction study (P295) conducted to investigate the co-administration of raltegravir and a magnesium/aluminium hydroxides liquid antacid. In addition, the MAH took the opportunity to move the paragraph on depression within section 4.4 of the SmPC. The MAH also proposes to reduce the text in Braille on the outer carton "Isentress 100 mg granules for oral suspension" to "Isentress 100 mg granules". C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	20/11/2014	19/11/2015	SmPC	The C12hr of steady-state raltegravir after staggered dosing of a single dose of a magnesium/aluminium antacid 4 or 6 hours before or after administration of raltegravir is decreased to a clinically meaningful degree as compared to raltegravir alone. The AUC0-12hr and Cmax of steady-state raltegravir after staggered dosing of a single dose of a magnesium/aluminium antacid 4 or 6 hours before or after administration of raltegravir is generally comparable though slightly decreased compared to raltegravir alone. Co-administration of Isentress with aluminium and/or magnesium containing antacids is not recommended.
PSUV/0049	Periodic Safety Update	09/10/2014	n/a		PRAC Recommendation - maintenance

X/0044/G	This was an application for a group of variations. Grouping of a line extension application to introduce a new pharmaceutical form (100 mg granules for oral suspension) and a type II variation to extend the indication to toddlers and infants from 4 weeks to less than 2 years of age. Consequently, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated and separate SmPC is introduced for the new pharmaceutical form. The Package Leaflet and Labelling are updated in accordance. In addition, minor updates are made to SmPC sections 5.1 and 6.1, Labelling and the PL. Furthermore, the product information is brought in line with the latest QRD version 9.3. 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	26/06/2014	22/08/2014	SmPC, Annex II, Labelling and PL	Please refer to the CHMP AR EMEA/H/C/000860/X/44/G.
R/0045	Renewal of the marketing authorisation.	20/03/2014	14/05/2014	SmPC, Labelling and PL	Based on the review of the available information and on the basis of a re-evaluation of the benefit risk balance, the CHMP was of the opinion that the quality, safety and efficacy of this medicinal product continues to be adequately and sufficiently demonstrated and therefore considered that the benefit risk profile of Isentress continues to be favourable. The CHMP was of the opinion that the renewal can be granted with unlimited validity.
II/0048	To change in-process test(s) and limits applied	25/04/2014	n/a		

	during the manufacture of the finished product B.II.b.5.e - Change to in-process tests or limits applied during the manufacture of the finished product - Widening of the approved IPC limits, which may have a significant effect on overall quality of the finished product				
II/0047	Update of section 4.5 of the SmPC with information on drug-drug interaction with boceprevir from study MK-3034-102. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	20/02/2014	14/05/2014	SmPC	Based on the results of study MK-3034-102 which evaluated the pharmacokinetic (PK) interaction between boceprevir and raltegravir, the CHMP concluded that no clinically meaningful interaction takes place between the two products.
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		
II/0042	Update of sections 4.4 and 4.5 of the SmPC with new information regarding the coadministration of Isentress with a calcium carbonate antacid and with an aluminium and magnesium hydroxide antacid following the availability of the results of Protocol 247 (P247), “A Study to Evaluate the Effect of Metal Cation Containing Antacids on Raltegravir Pharmacokinetics in HIV Infected Subjects on a Stable Raltegravir Containing Regimen.” Section 2 of the PL is updated accordingly. In addition, the MAH took the opportunity to update	25/07/2013	17/12/2013	SmPC, Annex II and PL	A drug interaction study in HIV-infected patients demonstrated no clinically significant interaction (defined as a reduction in raltegravir plasma trough concentration by >60%) between raltegravir and a calcium carbonate antacid but did show a clinically significant interaction with a magnesium/aluminium hydroxide antacid. This reduction likely results from the chelation of metal cations by raltegravir resulting in decreased absorption and diminished plasma concentrations, and possibly also pH-dependent effects of the antacid on raltegravir adsorption. Based on these results, a recommendation against co-

	the list of local representatives in the Package Leaflet, to amend contact details for the representative of the Czech Republic and Slovakia, and to include contact details for the representative of Croatia. Furthermore, the PI is being brought in line with the latest QRD template version 9. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				administration of raltegravir with aluminium and/or magnesium antacids has been added to the product information.
IB/0041	C.I.3.a - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under A 45/46, or amendments to reflect a Core SPC - Changes with NO new additional data are submitted by the MAH	24/05/2013	17/12/2013	SmPC and PL	To include in SmPC sections 4.4 and 4.8 information regarding autoimmune disorders under Immune Reactivation Syndrome, following a class labelling for all antiretrovirals as requested by the CHMP. The changes have also been reflected in the PL.
II/0040	Update of section 4.5 of the SmPC with information on drug interaction with boceprevir. Corrections of errors have been made in Section 4.5. In addition, the Annex II.B has been updated in line with the latest QRD template and the appearance of the 100mg chewable tablet was corrected in section 3 of the SmPC and 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	25/04/2013	17/12/2013	SmPC, Annex II and PL	Data from Study P08371 “Pharmacokinetic Study of the HCV Protease Inhibitor Boceprevir and the HIV Integrase Inhibitor Raltegravir (OPAL)” demonstrated that, when co-administered, no dose adjustment is required for Isentress or Victrelis.
X/0024/G	This was an application for a group of variations.	18/10/2012	25/02/2013	SmPC, Annex II, Labelling	Please refer to the Assessment Report: Isentress-H-860-X-

	Extension of Marketing Authorisation for Isentress chewable tablets 25 mg and 100 mg in the treatment of human immunodeficiency virus (HIV 1) infection in antiretroviral therapy (ART) experienced paediatric patients from the age of 2 years. Update of section 4.1 of the SmPC for the existing 400mg film-coated tablet with the new paediatric indication (adolescents and children from the age of 6 years) and introduce consequential changes to all sections of the SmPC for the existing 400mg film-coated tablet (except Sections 1 and 3), Annexes II, IIIA and IIIB. Changes to the product information were introduced in line with the QRD template. Annex I_2.(d) Change or addition of a new pharmaceutical form C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data			and PL	24-G-AR
II/0037	Update of sections 4.8 and 5.2 of the SmPC with the 240 weeks efficacy/safety data from the Phase III study (Protocol 021) in treatment naïve patients. The PL was updated in accordance. Annex II was updated in line with the latest QRD template. 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	17/12/2013	SmPC, Annex II and PL	STARTMRK / study 021 (multi-centre, randomised, double-blind, active-control trial) evaluates the safety and anti-retroviral activity of ISENTRESS 400 mg twice daily vs. SUSTIVA 600 mg at bedtime, in a combination with TRUVADA, in treatment-naïve HIV-infected patients. Primary efficacy results were previously reviewed by the CHMP (variations procedures II/10, II/17, II/25). The MAH presently complied with the request made by CHMP to submit the data through Week 240. The product information was updated with these long term safety (section 4.8) and efficacy data (section 5.1) on the use of

					ISENTRESS in treatment-naïve HIV-infected patients.
II/0035	Update of section 4.5 of the SmPC to include information regarding the effects of proton pump inhibitors and H2 antagonists on raltegravir safety and pharmacokinetics in HIV-positive patients. PL was updated accordingly. This submission is being made in fulfilment of Follow-Up Measure FU2 022.2. 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	17/12/2013	SmPC and PL	Study P054 was an open-label, 3-period, fixed-sequence study conducted at the CHMP request. The primary objective was to evaluate the effect of anti-acid treatments (on Isentress pharmacokinetics in HIV-infected adult subjects on a stable Isentress -containing ART regimen). This study demonstrated that co administration of Isentress with agents that increase gastric pH (proton pump inhibitors or H2 antagonists e.g., omeprazole and famotidine) may increase the rate of Isentress absorption and result in increased plasma levels of RAL. Safety profiles in the subgroup of patients taking proton pump inhibitors or H2 antagonists were comparable with those who were not taking these antacids. Therefore no dose adjustment is required with use of proton pump inhibitors or H2 antagonists.
IB/0039/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.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	21/12/2012	n/a		
II/0036	Update of section 4.5 of the SmPC with information on the potential drug drug interaction between darunavir and raltegravir following a request from the CHMP. The contact details for the local	15/11/2012	25/02/2013	SmPC and PL	Some clinical studies suggest that raltegravir (Isentress) may cause a modest decrease in darunavir (Prezista) plasma concentrations; the mechanism for this effect is unknown. However, the effect of raltegravir on darunavir

	representatives in Greece have been updated. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				plasma concentrations does not appear to be clinically meaningful. Isentress and darunavir co administered with low dose ritonavir can be used without dose adjustments.
IA/0038/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites	26/10/2012	n/a		
II/0033	Following the assessment of PSUR 8, update of section 4.8 of the SmPC with the term hepatic failure. In addition, update of section 4.4 to remove the reference to the very limited data on the use of raltegravir in patients co-infected with HIV and hepatitis B virus or hepatitis C virus following the availability of data from clinical studies. The PL is updated accordingly. 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	20/09/2012	25/10/2012	SmPC and PL	Following the assessment of PSUR 8 and a cumulative evaluation of post-marketing reports of hepatic failure received from initial market inception (27 September 2007) up to 29 February 2012, the term hepatic failure has been added to the product information (section 4.8 of the SmPC). Hepatic failure has been ranked as uncommon. In addition, following the availability of clinical studies data involving patients co-infected with HIV and hepatitis B virus or hepatitis C virus, the deletion of a reference to the limited dataset in this population was warranted in section 4.4 of the SmPC. For completeness the duration of the studies was also specified in section 4.8 of the SmPC.
IG/0182	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	20/08/2012	n/a		

II/0032	Update of section 5.2 of the SmPC to include information regarding the penetration of raltegravir into the cerebrospinal fluid. This submission is being made in fulfilment of Follow-Up Measure 046.1. In addition, the MAH took the opportunity to update the list of local representatives (Malta) in the PL. 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	21/06/2012	31/07/2012	SmPC and PL	In two investigator-initiated studies of HIV-1 infected patients who received raltegravir 400 mg twice daily, raltegravir was readily detected in the cerebrospinal fluid. In the first study (n=18), the median cerebrospinal fluid concentration was 5.8 % (range 1 to 53.5 %) of the corresponding plasma concentration. In the second study (n=16), the median cerebrospinal fluid concentration was 3 % (range 1 to 61 %) of the corresponding plasma concentration. These median proportions are approximately 3- to 6-fold lower than the free fraction of raltegravir in plasma.
IB/0030/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.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.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	21/03/2012	n/a		

	of the AS B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure				
II/0028	Update of section 4.4 of the SmPC to add caution in the use of raltegravir in patients with pre-existing depressive/psychiatric disorder following the assessment of PSUR 7. The Package Leaflet was updated accordingly. 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	16/02/2012	19/03/2012	SmPC and PL	Depression, including suicidal ideation and behaviors, has been reported, particularly in patients with a pre-existing history of depression or psychiatric illness. No new signal of concern is identified from the cases presented with the review of all cases relating to depression and suicidal ideation submitted with PSUR 7 (Period covered: 27.09.10 - 26.03.11). However, depression associated with Isentress continues to be an area of concern and the CHMP requested the MAH to continue to monitor cases of psychiatric disorders in future Periodic Safety Update Reports and to update the product information to add that caution should be used in patients with a pre-existing history of depression or psychiatric illness.
IA/0031	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)	07/03/2012	n/a		
II/0025	Update of sections 4.8 and 5.1 of the SmPC with the 156 weeks efficacy/safety data from the ongoing Phase III study (Protocol 021) in treatment naïve patients. Section 4 of the PL was updated accordingly. Updates to the Annex II.B and the details of the local representatives for Italy, Island and the Netherlands in the PL were also introduced.	19/01/2012	17/02/2012	SmPC, Annex II and PL	Study 021 is an ongoing double-blind, randomised, active-controlled, non-inferiority trial evaluating raltegravir 400 mg twice a day. versus efavirenz, each administered in combination with Truvada (tenofovir + emtricitabine). The primary efficacy endpoint was the proportion of patients achieving HIV RNA <50 copies/mL at Week 48 with a secondary efficacy endpoint at Week 96. The study extension allows for continued blinded observations

	C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				through Week 240. The Week 156 data submitted with the present application confirm the safety or efficacy of raltegravir. Sections 4.8 and 5.1 of the SmPC with were updated with this new information.
II/0022	Update of section 4.4 with severe skin and hypersensitivity reactions and section 4.8 of the SmPC with the term "Drug rash with eosinophilia and systemic symptoms" (DRESS) based upon post-marketing reports received by the MAH and a cumulative review of severe hypersensitivity disorders including DRESS and cases suggestive of DRESS following the review of PSUR 6. The PL is being updated accordingly. The list of local representatives is also updated. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	20/10/2011	21/11/2011	SmPC and PL	An analysis of post-marketing reports on DRESS identified ten reports including two with positive dechallenge and no reported treatment with other drugs for which DRESS is listed as an adverse reaction. A cumulative review of severe hypersensitivity disorders including DRESS identified 12 reports, including three cases with positive dechallenge for raltegravir, one of which also had a positive rechallenge. One other case had a plausible temporal relationship to treatment with antiretrovirals, including raltegravir, but dechallenge was negative. A cumulative review of severe hypersensitivity disorders including cases suggestive of DRESS identified 17 reports. One case of eosinophilia with no other terms suggestive of DRESS and one case of toxic skin eruption, where the patient had a rash and fever but no eosinophilia, were identified. Two other cases involved severe hypersensitivity. Based on this information, a warning regarding severe skin and hypersensitivity reactions was added in section 4.4 of the SmPC and DRESS was added as a new ADR in section 4.8 of the SmPC. Hypersensitivity is already listed in the product information for raltegravir. No further action with regard to severe skin disorders is required at present. However, the CHMP requested that these ADRs should continue to be monitored closely by the MAH. Based on the data from the cumulative review and the addition of a warning in the SmPC, severe skin reactions should be upgraded to an important identified risk in the

					next RMP update.
IG/0112	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	11/10/2011	n/a		
N/0023	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	18/08/2011	n/a	PL	
IA/0021	A.4 - Administrative change - Change in the name and/or address of a manufacturer or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS	17/12/2010	n/a		
IG/0027/G	This was an application for a group of variations. 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.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	10/11/2010	n/a	Annex II	
II/0019	Update of section 4.8 of the SmPC with the adverse reaction "thrombocytopenia" with a frequency of "uncommon" as requested by the CHMP following the assessment of PSUR 4. C.I.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a	22/07/2010	31/08/2010	SmPC	During the period of review for the PSUR 4 (Period covered: 27.03.09 - 26.09.09), six cases of thrombocytopenia were identified. As a result, the MAH was requested to submit a variation to include thrombocytopenia as an adverse reaction (ADR). A cumulative review of spontaneous and study cases of thrombocytopenia through 28 February 2010 identified 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				total of 25 reports with sufficient information for assessment. In many of these cases, the aetiology of the thrombocytopenic event was not entirely clear. Several of the cases reported past medical history and/or concurrent conditions. In addition, many patients started other antiretroviral agents at, or around, the same time as raltegravir. However, good temporal relationships were seen in some of the cases and several cases reported a positive dechallenge after raltegravir withdrawal. Moreover, one case reported a positive rechallenge which indicates a probable causal relationship between raltegravir and thrombocytopenia. Therefore, the term "thrombocytopenia" with a frequency of "uncommon" is included in the table of ADRs in section 4.8 of the raltegravir SmPC.
II/0018	Update of section 4.8 of the SmPC based on post marketing data to add the term "rhabdomyolysis" with the frequency "uncommon". In line with the SmPC guideline, the frequency category of the ADRs identified in the post-marketing period "Stevens-Johnson Syndrome" and "Suicidal ideation and suicidal behaviour" is changed from "not known" to "uncommon". A footnote is added to the table of ADRs in section 4.8 to explain how the frequencies are calculated for these ADRs. Finally, some minor changes to section 4.4 and 4.8 are introduced in line with the SmPC guideline. The PL is updated in accordance. Update of Summary of Product Characteristics and Package Leaflet	22/07/2010	31/08/2010	SmPC and PL	The MAH provided 61 reports identified from a cumulative evaluation of reports of increase in creatine kinase with clinical manifestations, myopathy, and rhabdomyolysis, among patients treated with raltegravir, received from September 2007 to September 2009, including all postmarketing reports and clinical study reports. Of the 61 reports, there were 18 reports of blood creatine phosphokinase increased and 19 reports of rhabdomyolysis, one of which involves a positive rechallenge. Several of the cases are difficult to assess due to the presence of pre-existing events which put the patient at increased risk of rhabdomyolysis, other drugs associated with rhabdomyolysis or because the patient started and stopped several antiretroviral agents at the same time. However, causality with raltegravir in these cases cannot be excluded.

					In line with the advice from the SmPC guideline (revision 2, September 2009), this adverse reaction (ADR) is included with a frequency of "uncommon". Also in line with this guideline, the frequency category of the ADRs identified in the post-marketing period "Stevens-Johnson Syndrome" and "Suicidal ideation and suicidal behaviour" is changed from "not known" to "uncommon".
IA/0020	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)	18/06/2010	n/a		
II/0016	Addition of MSD facility in SIngapore as an alternate manufacturing site and an alternate analytical release testing site for Raltegravir tablets Quality changes	22/04/2010	30/04/2010		
II/0017	Update of sections 4.1, 4.4, 4.8 and 5.1 of the SmPC based on the 96 week update of study protocols 18, 19 and 21 in line with follow-up measure (FUM) 016.1. In addition, the MAH took this opportunity to update information on the co-administration with darunavir/ritonavir and the risk of rash in line with the CHMP's request of FUM 006.1. The PL was updated in accordance. Update of Summary of Product Characteristics and Package Leaflet	18/02/2010	26/03/2010	SmPC and PL	The additional safety and efficacy data (week 96) generally confirm the previous conclusions regarding raltegravir use in antiretroviral-experienced and naïve patients. The Week 96 data show that the majority of patients who had responded at Week 24 and/or week 48 maintained their virological response to Week 96 and a benefit for raltegravir over placebo and non- inferiority to efavirenz was confirmed. In this follow-up including Weeks 48 to 96 of the 3 pivotal studies 018, 019 and 021 in treatment experienced and naïve patients, no new safety concerns were identified. The updated clinical data provide further assurance that there does not appear to be any specific cancer risk associated with raltegravir.

II/0010	To extend the indication to include antiretroviral therapy naïve adult patients. Extension of Indication	23/07/2009	09/09/2009	SmPC, Annex II and PL	Please refer to the Assessment Report: Isentress-H-860-II-10-AR
II/0014	Update of the Detailed Description of the Pharmacovigilance System (DDPS). Annex II has been updated to reflect the version number of the DDPS. Update of DDPS (Pharmacovigilance)	25/06/2009	16/07/2009	Annex II	The MAH updated its DDPS and submitted therefore this type II variation. The CHMP considers that the Pharmacovigilance System as described by the MAH fulfils the requirements and is considered acceptable.
SW/0013	Switch from conditional to full Marketing Authorisation	29/05/2009	14/07/2009		
II/0012	Addition of a new manufacturer for the active substance. This new manufacturer will use a new synthetic route (designated as "third generation synthesis") and an alternate container closure sytem for the Drug Substance. Quality changes	29/05/2009	11/06/2009		
II/0009	Update of section 5.3 of the SPC based on long-term (2-year) carcinogenicity studies of raltegravir in rodents in fulfilment of a post-authorisation commitment. Update of Summary of Product Characteristics	23/04/2009	28/05/2009	SmPC	The study in mice showed no evidence of carcinogenicity at any raltegravir dose levels tested. In rats, tumours (squamous cell carcinoma) of the nose / nasopharynx were identified in high and intermediate dose group animals. These neoplasms were considered to be secondary to chronic irritation and inflammation, also present within the nasopharynx and nose, and a consequence of reflux

					aspiration of the study drug. Raltegravir was negative in a series of genotoxicity and clastogenicity studies. The data did not indicate a relevant risk of carcinogenicity for humans.
II/0011	Update of section 4.8 of the SPC based on postmarketing experience information reported within PSUR 2. Consequently, the PL was updated. Update of Summary of Product Characteristics and Package Leaflet	19/03/2009	21/04/2009	SmPC and PL	In the period since first marketing to 28 September 2008, 17 reports of depression and 9 reports with a term relating to suicidality in association with raltegravir were reported. Even though some reports were confounded by the patients' condition and concomitant medication, in some cases causal association to raltegravir could not be excluded. Depression, which was observed with raltegravir in randomised clinical trials, is already listed as an uncommon psychiatric disorder. Suicidal ideation and behaviours (particularly in patients with a pre-existing history of psychiatric illness) were now added to the SPC under the Psychiatric Disorders section with a frequency of "unknown".
II/0001	Update of sections 4.1, 4.5, 4.8 and 5.1 of the SPC based on 48 week safety and efficacy data from two pivotal clinical studies, as well as the long-term safety data from ongoing Phase II studies. Consequently, the PL and Annex II were updated. In addition, the MAH took the opportunity to update section 4.5 of the SPC in line with the CHMP assessment of Follow-Up Measure 005 to include pharmacokinetic interaction data from a study on the effect of raltegravir on oral contraceptive pharmacokinetics in females. Furthermore, the	20/11/2008	07/01/2009	SmPC, Annex II and PL	As a Specific Obligation (SOB), the MAH committed to provide the CHMP with the 48-week safety and efficacy data from the ongoing Phase III Protocol 018 and Protocol 019 for review to further support the benefit/risk assessment. The MAH has provided this data as a part of this variation in order to fulfil the above SOB, as well as pharmacokinetics and long-term safety data from ongoing Phase II studies. The pharmacokinetics data presented in this variation, in particular in relation to concomitant medications gave a clearer picture of the interactions. Section 4.5 of the SPC was updated to include that raltegravir did not have a

	details of the local reprersentatives of Iceland and Malta were updated in the PL. Update of Summary of Product Characteristics and Package Leaflet				clinically meaningful effect on the pharmacokinetics of hormonal contraceptives and to include the related pharmacokinetics data. The submitted pharmacokinetics data further warranted the mentioning of the effect of less potent UGT1A1 inhibitors such as indinavir and saquinavir in the SPC. The data further supported an update of the existing pharmacokinetic interaction data for tenofovir and omeprazole. In terms of efficacy, the 48-weeks data overall confirmed the effects assessed for the initial Marketing Authorisation, however the SPC was updated with the efficacy outcomes at week 48 to replace the 24-weeks data. In addition, the analysis gave further information in terms of virologic responses and viral rebound up to week 48, which was also included in the SPC. The safety data submitted for this variation overall confirmed the previously observed safety profile, however the longer term data warranted inclusions of further adverse events (rash-related events), in the SPC. Furthermore, also previously not included non-severe AEs that occurred at a rate < 1% were listed in the Product Information together with other changes in line with the current guidance.
R/0008	Renewal of the marketing authorisation.	25/10/2008	19/11/2008	Annex II	The CHMP reviewed the available information on the status of the fulfilment of the Specific Obligations by the MAH. The Committee confirmed that the quality, safety and efficacy of this medicinal product continue to be adequately and sufficiently demonstrated, and that its benefit risk balance

					remains positive. The Committee recommended that the Marketing Authorisation remains 'conditional' until the remaining specific obligations are fulfilled.
II/0007	Update of section 4.8 of the SPC based on postmarketing experience information reported in PSUR 1 (covering the period of 27 September 2007 to 26 March 2008). Consequently, the PL was updated. Update of Summary of Product Characteristics and Package Leaflet	24/07/2008	28/08/2008	SmPC and PL	Furthe to the post-marketing reports of rash and Stevens-Johnson syndrome, a relationship between raltegravir therapy and the occurrence of these adverse drug reactions could not be excluded. Therefore, both SPC and PL were updated regarding these skin and subcutaneous skin disorders. The MAH will have to monitor both skin and hypersensitivity reactions in the upcoming Periodic Safety Update Reports (PSUR).
IB/0006	IB_12_b_02_Change in spec. of active subst./agent in manuf. of active subst. - test parameter	27/08/2008	n/a		
IB/0005	IB_12_b_02_Change in spec. of active subst./agent in manuf. of active subst. - test parameter	27/08/2008	n/a		
IB/0004	IB_13_b_Change in test proc. for active substance - other changes (replacement/addition)	08/07/2008	n/a		
IB/0003	IB_13_b_Change in test proc. for active substance - other changes (replacement/addition)	08/07/2008	n/a		
IB/0002	IA_36_ b_Change in shape or dimensions of the container/closure - other pharm. forms IB_14_b_Change in manuf. of active substance without Ph. Eur. certificate - new manufacturer	08/07/2008	n/a		