Edurant

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
X/0042/G	This was an application for a group of variations. 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	25/07/2024	19/09/2024	SmPC, Annex II, Labelling and PL	For further information please refer to the published Assessment Report: Edurant H-2264-X-42-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).

	modification of an approved one Annex I_2.(c) Change or addition of a new strength/potency Extension application to introduce a new pharmaceutical form associated with new strength (2.5 mg dispersible tablets). The new presentation ,in combination with other antiretroviral medicinal products, is indicated for the treatment of human immunodeficiency virus type 1 (HIV 1) infection in paediatric patients 2 to less than 18 years of age and weighing at least 14 kg to less than 25 kg without known mutations associated with resistance to the non-nucleoside reverse transcriptase inhibitor (NNRTI) class, and with a viral load ≤ 100,000 HIV 1 RNA copies/ml (see sections 4.4 and 5.1). Genotypic resistance testing should guide the use of EDURANT (see sections 4.4 and 5.1).The PI and RMP have been updated in accordance. Type II variation (C.I.6.a) to modify the approved therapeutic indication of the already authorised 25 mg film-coated tablets presentation for the treatment of human immunodeficiency virus type 1 (HIV 1) infection in adults and paediatric patients weighing at least 25 kg without known mutations associated with resistance to the non-nucleoside reverse transcriptase inhibitor (NNRTI) class, and with a viral load ≤ 100,000 HIV 1 RNA copies/ml in combination with other antiretroviral medicinal products. (see sections 4.4 and 5.1). Genotypic resistance testing should guide the use of EDURANT				

	(see sections 4.4 and 5.1). This is based on final results from study studies TMC278-TiDP38-C213 Cohort 2. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2, 5.3 and 6.4 of the SmPC are updated. The Package Leaflet and Labelling are updated in accordance. The updated RMP version 10.1 has also been submitted. In addition, the MAH took the opportunity to implement editorial changes including Annex II and the list of local representatives in the Package Leaflet.				
IB/0041	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	28/10/2022	09/10/2023	SmPC and PL	
PSUSA/9282/ 202105	Periodic Safety Update EU Single assessment - rilpivirine (for oral use)	13/01/2022	n/a		PRAC Recommendation - maintenance
IB/0038	B.II.f.1.b.2 - Stability of FP - Extension of the shelf life of the finished product - After first opening (supported by real time data)	10/08/2021	08/07/2022	SmPC, Labelling and PL	Change to the local representative for the United Kingdom (UK).
II/0037	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	16/01/2020	n/a		
II/0036	Update section 4.6 of the SmPC based on the most recent data described in the ARV Pregnancy Registry (APR). In addition, the Marketing authorisation holder (MAH) took the opportunity to update the Package Leaflet to include information on the sodium excipient, as per the revised Annex to the European	12/12/2019	16/11/2020	SmPC and PL	Data from the ARV Pregnancy Registry (APR) (between 300-1000 pregnancy outcomes) showed no malformative or feto/neonatal toxicity of rilpivirine (RPV). Based on this information, the use of RPV may be considered during pregnancy, if necessary.

	Commission guideline on 'Excipients in the labelling and package leaflet of medicinal products for human use' and the list of local representatives, as well as to make minor editorial changes in the SmPC and in the Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
II/0035	Update of section 5.1 of the SmPC to reflect the week 240 results from the TMC278-TiDP38-C213(C213) study a phase II, open-label, single-arm trial to evaluate the pharmacokinetics, safety, tolerability, and antiviral activity of rilpivirine in antiretroviral-naïve HIV-1 infected adolescents and children aged ≥6 to <18 years, upon request by CHMP following the assessment of the paediatric study C213 submitted according to Art. 46 procedure (no. EMEA/H/C/2264/P46/028). In addition, the Marketing authorisation holder (MAH) took the opportunity to update Section 4.8 of the SmPC to indicate that no safety concerns were identified in the Week 240 analysis of the C213 trial in adolescents aged ≥12 to <18 years. Editorial changes have also been made to the product information. C.I.3.z - 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 - Other variation	19/09/2019	17/10/2019	SmPC	Results of the week 240 Study TMC278-TiDP38-C213 (C213) showed that rilpivirine resistance-associated mutations (RAMs) were observed in 46.7% (7/15) of subjects with virologic failure and post-baseline genotypic data. All subjects with rilpivirine RAMs also had at least 1 treatment-emergent NRTI RAM at the last post-baseline time point with genotypic data.

II/0034	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	14/06/2019	n/a		
IA/0033/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 B.III.2.b - Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State - Change to comply with an update of the relevant monograph of the Ph. Eur. or national pharmacopoeia of a Member State	29/04/2019	n/a		
II/0032	Update of section 4.9 of the SmPC to remove the advice on the use of activated charcoal in the event of an overdose and to include advice to contact a poison control centre to obtain the latest recommendations for the management of an overdose. The requested variation proposed amendments to the Summary of Product Characteristics. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	31/01/2019	17/10/2019	SmPC	Given the lack of evidence for the clinical benefit of the use of activated charcoal in the event of rilpivirine overdose, section 4.9 of the SmPC is being updated to delete the recommendation that active charcoal may be used to aid in removal of unabsorbed active substance, and include the recommendation that it is advisable to contact a national poison control centre.

PSUSA/9282/ 201805	Periodic Safety Update EU Single assessment - rilpivirine (for oral use)	17/01/2019	n/a		PRAC Recommendation - maintenance
IG/0980	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	24/10/2018	17/10/2019	SmPC and PL	
N/0029	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	11/04/2018	17/10/2019	PL	
N/0027	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	19/02/2018	17/10/2019	PL	
IAIN/0028	B.I.a.1.a - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer	15/02/2018	n/a		
II/0024	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	06/07/2017	24/08/2017	SmPC and PL	
II/0025	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	06/07/2017	24/08/2017	SmPC and Labelling	
IA/0026	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	18/04/2017	n/a		

R/0022	Renewal of the marketing authorisation.	26/05/2016	22/07/2016	SmPC, Annex II, Labelling and PL	Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of Edurant in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity. Amendments to Annexes I, II, IIIA and IIIB are made to implement changes in line with the current QRD template version 10. In addition, Edurant (rilpivirine) is being removed from the additional monitoring list, therefore the statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information, preceded by an inverted equilateral black triangle, is removed from the summary of product characteristics and the package leaflet.
N/0023	Update of the package leaflet with revised contact details of the local representatives for Estonia, Lithuania, Latvia, Romania and Sweden. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	22/04/2016	22/07/2016	PL	
WS/0872	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	28/01/2016	22/07/2016	SmPC and PL	
PSUSA/9282/ 201505	Periodic Safety Update EU Single assessment - rilpivirine (for oral use)	03/12/2015	n/a		PRAC Recommendation - maintenance

II/0017/G	This was an application for a group of variations. Extension of Indication to include treatment of antiretroviral treatment-naïve paediatric patients aged 12 to <18 years of age based on the results of the 48-week data of study TMC278-TiDP38-C213 (PAINT), undertaken to evaluate the pharmacokinetics, safety/ tolerability, and efficacy of rilpivirine 25 mg qd in combination with an investigator-selected background regimen containing two nucleoside (nucleotide) reverse transcriptase inhibitors (NRTIs) in this adolescent population. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC have been updated and the Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to update the contact details of the local representative in Denmark in the Package Leaflet. A revised RMP version 6.1 was agreed during the procedure. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing	22/10/2015	20/11/2015	SmPC and PL	For further information please refer to the published Assessment Report: Edurant H-2264-II-17-G-AR.

	authorisation, including the RMP - Other variation C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation				
IA/0019/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 B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	24/07/2015	n/a		
PSUSA/9282/ 201411	Periodic Safety Update EU Single assessment - rilpivirine (for oral use)	11/06/2015	n/a		PRAC Recommendation - maintenance
IAIN/0018/G	This was an application for a group of variations. A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site 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.2.a - Change to importer, batch release	06/05/2015	n/a		

	arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place				
II/0015	Submission of the Clinical Study Report of the EDURANT/EVIPLERA Health Care Professional Survey - MEA 011.3 – undertaken to gain an understanding of the effectiveness of the current prescribing conditions in minimising the risk associated with taking the products without food/a meal, potentially associated with the risk of development of drug resistance. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	23/04/2015	n/a		N/A
PSUV/0014	Periodic Safety Update	04/12/2014	n/a		PRAC Recommendation - maintenance
PSUV/0012	Periodic Safety Update	13/06/2014	n/a		PRAC Recommendation - maintenance
WS/0507	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Worksharing procedure for Prezista, Intelence and Edurant to update section 4.4 of the SmPC with a revised wording on the risk of transmission. The PL has been updated accordingly. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	20/03/2014	01/09/2014	SmPC and PL	During recent years conclusive evidence has been collected which shows that the risk for HIV patients, who are well treated, to sexually transmit HIV to their partner is exceedingly low. A position statement on the use of antiretroviral therapy to reduce HIV transmission was published by the British HIV Association (BHIVA) in January 2013. As a consequence, the recommendations for post-exposure prophylaxis have also been changed in recently updated HIV treatment guidelines. For example, the 2013 BHIVA guideline does not generally recommend post-exposure prophylaxis (PEP) after exposure from a patient

					with well treated HIV. Based on these data, the wording on the risk of transmission for HIV products was revised to reflect the current scientific knowledge. While effective suppression with antiretroviral therapy has been proven to substantially reduce the risk of sexual transmission, a residual risk cannot be excluded. Precautions to prevent transmission should be taken in accordance with national guidelines.
IB/0011/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	20/03/2014	n/a		
II/0010	Update of section 4.5 of the SmPC with information on interactions between rilpivirine and metformin according to the results of a drug interaction study performed to fulfil a Post-Authorization Measure. Based on an in vitro test this section was further updated with the information that rilpivirine is an in vitro inhibitor of the transporter MATE-2K with an IC50 of <2.7 nM and that the clinical implications of this finding are currently unknown. The package leaflet was revised accordingly and the MAH proposed to update the contact details of the local representatives. Furthermore, the MAH introduced an administrative correction to the address of the manufacturer both in annex II and in	18/12/2013	01/09/2014	SmPC, Annex II and PL	Rilpivirine has been shown to inhibit OCT2 in vitro. At the time of the study set up, no information on the effect of rilpivirine on MATE transporters was known. The current study was designed to assess the effect of steady-state rilpivirine on OCT2 in vivo, by evaluating its effect on the pharmacokinetics of the OCT2 substrate, metformin, in healthy adult subjects. The study showed that rilpivirine 25 mg q.d. had no effect on the plasma pharmacokinetics of metformin and its urine clearance. An in vitro test showed that rilpivirine is an in vitro inhibitor of the transporter MATE-2K with an IC50 of <2.7 nM and that the clinical implications of this finding are currently unknown.

	the PL. Also a minor editorial change was made to section 4.9 of the SmPC. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
II/0008	To update section 4.2, 4.3 and 4.5 of the SmPC regarding rilpivirine-rifabutin interaction after the completion of the study TMC278IFD1003, with the finding that under rifabutin treatment rilpivirine can be used concomitantly (previously contraindicated) if an additional dose of 25 mg rilpivirine is taken. The package leaflet was updated accordingly. Furthermore, the MAH took the opportunity to bring the PI in line with the latest QRD template version, including the black symbol and explanatory statements for medicines under additional monitoring. Other minor revisions made were correcting the values at week 96 of the 'basal cortisol mean change from baseline' in SmPC section 4.8 and rewording for greater clarity in SmPC section 5.1 how in vitro resistance is determined. In addition the list of representatives in the leaflet was updated to add Croatia. The requested variation proposed amendments to the Summary of Product Characteristics and 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	19/09/2013	01/09/2014	SmPC and PL	The interaction study TMC278IFD1003, which was requested at the time of the Marketing Authorisation, showed that after administration rifabutin 300 mg q.d. and 25 mg q.d. rilpivirine, the AUC, Cmax and Cmin for rilprivirine decreased by 42, 31 and 48%, respectively while an increase in the rilpivirine dose to 50 mg q.d. lead to an increase of rilpivirine AUC and Cmax of about 16 and 42%, while Cmin decreased 7%. The observed differences, compared to a 25 mg q.d. dose of rilpivirine, were considered safe and efficacious and it was considered that a rilpivirine dose of 50 mg q.d could compensate for the inducing effect of rifabutin. The CHMP therefore agreed that the contraindication for coadministration of Edurant with rifabutin could be replaced with a warning in SmPC section 4.4 and instructions in SmPC sections 4.2 and 4.5 stating that when Edurant is co-administered with rifabutin, an additional 25 mg tablet of rilpivirine per day is recommended to be taken concomitantly with Edurant, for the duration of the rifabutin co-administration.

IG/0341	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	31/07/2013	n/a		
WS/0396	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of sections 4.4 and 4.8 of the SmPC in order to update the safety information regarding autoimmune disorders in relation to Immune Reactivation Syndrome, following a class labelling for antiretrovirals as requested by the CHMP. The Package Leaflet was updated accordingly. In addition, the WSA took the opportunity to update the list of local representatives in the Package Leaflet. 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	30/05/2013	21/06/2013	SmPC and PL	Upon review of safety data and literature on immune disorders in association with antitretrovirals for the treatment of HIV, the CHMP considered that there is sufficient evidence to conclude that immune reconstitution syndrome (IRS) after antiretroviral therapy may be associated with autoimmune disease/disorders even if the number of case reports is limited. Therefore, the CHMP had requested the inclusion of information on immune disorders under immune reconstitution as a class labelling for all antiretrovirals for the treatment of HIV.
II/0006	Update of section 4.5 of the SmPC with results of a drug-drug interaction study between rilpivirine and digoxin (study TMC278IFD1001). Section 4.5 of the SmPC was also updated to remove the reference to the interaction with 'troleandomycin' as it is no longer marketed in the EU. The Package Leaflet was updated accordingly. The MAH has also introduced minor editorial changes in section 4.5. Furthermore, Annex II was brought in line with the latest QRD	21/02/2013	21/06/2013	SmPC, Annex II and PL	Rilpivirine has P-glycoprotein (P-gp) inhibitory properties in vitro with an apparent half maximum inhibitory concentration (IC50) value of 3.4 µg/ml. While rilpivirine plasma concentrations in healthy volunteers and in HIV-1 infected patients are below this level, theoretically the intestinal concentration of rilpivirine after administration of a 25 mg oral dose could be up to 100 µg/ml. Therefore rilpivirine could potentially affect the pharmacokinetics of P-gp substrates.

	template version 8.3. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				The results from study TMC278IFD1001 demonstrated that the pharmacokinetics of the P-gp substrate digoxin is not affected by rilpivirine, administered at the recommended 25 mg daily dose. This was further substantiated by urinary excretion data. However, the CHMP noted that digoxin is not very sensitive to inhibition of intestinal P-gp, thus it cannot be concluded that there is no effect of rilpivirine on more sensitive substrates of intestinal P-gp, such as dabigatran etexilate. This information was included in section 4.5, and the reference to troleandomycin was deleted as this product is no longer marketed in the EU.
II/0005	Update of section 5.1 of the SmPC in order to include Y188L as a rilpivirine resistance-associated mutation (RAM). Following CHMP request annex II of the product information was updated according to the QRD template version 8, revision 2. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	13/12/2012	21/06/2013	SmPC and Annex II	The association of decreased susceptibility to Rilpivirine due to baseline RAM Y188L has been confirmed in analysis of data from a database of clinical specimens and site-directed mutagenesis studies and spontaneous individual case report. Section 5.1 of the SmPC is updated accordingly.
II/0003	Update of section 4.5 of the SmPC on interaction with raltegravir. This Type II Variation is submitted to fulfill the following Post-Authorisation measure: MEA002. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	20/09/2012	24/10/2012	SmPC	Raltegravir is eliminated mainly by metabolism via a uridine glucuronyl-transferase (UGT) 1A1-mediated pathway (main [inactive] metabolite: raltegravir glucuronide). Raltegravir has a low propensity for causing drug interactions with substrates of CYP enzymes (such as rilpivirine) as it is not a substrate, an inhibitor, or an inducer of CYP enzymes. Rilpivirine is a substrate of CYP3A and is unlikely to affect metabolic enzymes (including UGT) to a clinically relevant extent. No interaction is expected. This is confirmed in the currently submitted phase I study,

					based on data obtained in 23 subjects.
II/0002	Update of section 4.5 of the SmPC on interactions between rilpivirine and telaprevir. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	20/09/2012	24/10/2012	SmPC	Rilpivirine is a substrate of CYP3A, therefore plasma concentrations of rilpivirine could be increased when coadministered with telaprevir. This is confirmed in the currently submitted phase I study in healthy volunteers. Including the results of all subjects, the data showed that rilpivirine AUC, Cmax and Cmin increased 78, 49 and 93%, respectively due to co-administration of telaprevir 750 mg thrice daily. However, rilpivirine did not affect the plasma concentrations of telaprevir. Although plasma concentrations of rilpivirine increased, it is agreed that no dose adjustment is required.
II/0001/G	This was an application for a group of variations. The MAH proposed the update of sections 4.1, 4.4, 4.8 and 5.1 of the SmPC to reflect the 96 weeks results of the pivotal studies C209 and C215 and the results of the 240 weeks of phase IIb trial 204. The MAH took the opportunity of this update to include in sections 8 and 9 of the SmPC the marketing authorization number and the date of the first marketing authorization respectively. The PL was updated to reflect the new data. In addition, the MAH proposed to update the list of local representatives in the Package Leaflet. Furthermore, the MAH proposed this opportunity to bring the PI in line with the latest QRD template version and to correct spelling mistakes. The requested group of variations proposed amendments to the SmPC, Annex II, labelling and Package Leaflet.	20/09/2012	24/10/2012	SmPC, Annex II, Labelling and PL	Results of the pivotal studies C209 and C215 confirmed the non-inferior virological efficacy of RPV 25 mg once daily over 96 week in the approved indication. Similar results were observed for the FTC/TDF backbone which is the background regimen in the fixed dose combination. Week 96 data confirm the safety of the product, no additional safety warnings became apparent after week 48. 240 week results of phase IIb trial 204 confirm the safety of the product. The benefit risk of the product remains positive.

	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				
IG/0213	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	28/08/2012	n/a		