Celsentri

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
IAIN/0070	A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release	02/12/2024		Annex II and PL	
IB/0068/G	This was an application for a group of variations.	01/10/2024		SmPC, Labelling and	

[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).

	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 parameter) B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits B.II.e.1.b.3 - Change in immediate packaging of the finished product - Change in type/addition of a new container - Deletion of an immediate packaging container without a complete deletion of a strength or pharmaceutical form B.II.e.1.b.3 - Change in immediate packaging of the finished product - Change in type/addition of a new container - Deletion of an immediate packaging container without a complete deletion of a strength or pharmaceutical form B.II.e.1.b.3 - Change in immediate packaging of the finished product - Change in type/addition of a new container - Deletion of an immediate packaging container without a complete deletion of a strength or pharmaceutical form B.II.e.1.b.3 - Change in immediate packaging of the finished product - Change in type/addition of a new container - Deletion of an immediate packaging container without a complete deletion of a strength or pharmaceutical form 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			PL	

	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 B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.c.1.z - Change in the specification parameters and/or limits of an excipient - Other variation				
IB/0069/G	This was an application for a group of variations. B.I.b.2.z - Change in test procedure for AS or starting material/reagent/intermediate - Other variation B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder	01/08/2024	n/a		

	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.c.2.b - Change in the specification parameters and/or limits of the immediate packaging of the AS - Addition of a new specification parameter to the specification with its corresponding test method B.I.d.1.a.4 - Stability of AS - Change in the re-test period/storage period - Extension or introduction of a re-test period/storage period supported by real time data B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.c - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure for a reagent, which does not have a significant effect on the overall quality of the AS B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.b.2.b - Change in test procedure for AS or starting material/reagent/intermediate - Deletion of a test procedure for the AS or a starting material/reagent/intermediate, if an alternative test				

	procedure is already authorised B.I.b.2.b - Change in test procedure for AS or starting material/reagent/intermediate - Deletion of a test procedure for the AS or a starting material/reagent/intermediate, if an alternative test procedure is already authorised A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites				
IG/1531	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	19/08/2022	15/09/2023	SmPC and PL	
PSUSA/1934/ 202108	Periodic Safety Update EU Single assessment - maraviroc	10/03/2022	n/a		PRAC Recommendation - maintenance
N/0065	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	15/09/2021	15/09/2023	PL	
IB/0064	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	07/09/2020	09/10/2020	SmPC, Annex II, Labelling and PL	
IB/0063	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	28/07/2020	n/a		
IG/1237	A.1 - Administrative change - Change in the name and/or address of the MAH	11/06/2020	09/10/2020	SmPC, Labelling and	

				PL	
II/0061	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	12/03/2020	n/a		
IB/0060	B.II.f.1.b.1 - Stability of FP - Extension of the shelf life of the finished product - As packaged for sale (supported by real time data)	01/10/2019	09/10/2020	SmPC	
IB/0059	B.II.b.4.z - Change in the batch size (including batch size ranges) of the finished product - Other variation	25/07/2019	n/a		
PSUSA/1934/ 201808	Periodic Safety Update EU Single assessment - maraviroc	14/03/2019	n/a		PRAC Recommendation - maintenance
IAIN/0057/G	This was an application for a group of variations. B.II.e.1.a.1 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Solid pharmaceutical forms B.II.e.7.a - Change in supplier of packaging components or devices (when mentioned in the dossier) - Deletion of a supplier C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	11/10/2018	01/10/2019	SmPC	
T/0056	Transfer of Marketing Authorisation	14/09/2018	28/09/2018	SmPC, Labelling and PL	
II/0054/G	This was an application for a group of variations.	12/04/2018	28/09/2018	SmPC and PL	In this variation the MAH has updated the Product Information with information on maraviroc metabolism and

	Update of sections 4.5 and 5.2 of the SmPC in order to update the data regarding drug metabolising enzymes and drug transporters from several completed in vitro studies and to support the addition of pharmacogenomic information based on final results from study (A4001110), respectively. Furthermore, section 5.1 has been updated with information on genotypic resistance. Additionally, minor changes have been introduced in 4.2, 4.4, and 5.1 sections of the SmPC. The Package Leaflet section on How to measure the dose and take the medicine has been updated to further clarify the instructions. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				interactions based on in vitro and clinical studies. Maraviroc is a substrate for the transporters P-glycoprotein and OAT1B1, but the effect of these transporters on the exposure to maraviroc is not known. In vitro studies have shown that maraviroc does not inhibit OATP1B1, MRP2 or any of the major P450 enzymes at clinically relevant concentrations. In vitro studies have also shown that maraviroc does not inhibit any of the major renal uptake transporters at clinically relevant concentrations (OAT1, OAT3, OCT2, OCTN1, and OCTN2). The pharmacokinetics of maraviroc is dependent on CYP3A5 activity and expression level, which can be modulated by genetic variation. The CYP3A5 allelic frequency depends on ethnicity: the majority of Caucasians (~90%) are poor metabolisers of CYP3A5 substrates (i.e., subjects with no copy of functional CYP3A5 alleles) while approximately 40% of African-Americans and 70% of Sub-Saharan Africans are extensive metabolisers (i.e., subjects with two copies of functional CYP3A5 alleles). In a Phase 1 study conducted in healthy subjects all achieved the average concentrations that have been shown to be associated with near maximal virologic efficacy with maraviroc (75 ng/mL) in the Phase 3 study in treatment naïve adult patients (MERIT). Therefore, despite differences in CYP3A5 genotype prevalence by race, the effect of CYP3A5 genotype on maraviroc exposure is not considered clinically significant and no maraviroc dose adjustment according to CYP3A5 genotype, race or ethnicity is needed. Furthermore, information on the genotypic resistance has been updated as follows: A relatively small number of individuals receiving maraviroc-containing therapy have failed with phenotypic

					resistance (i.e. the ability to use drug-bound CCR5 with MPI <95%). To date, no signature mutation(s) have been identified. The gp120 amino acid substitutions identified so far are context dependent and inherently unpredictable with regards to maraviroc susceptibility.
IB/0055	B.II.f.1.b.1 - Stability of FP - Extension of the shelf life of the finished product - As packaged for sale (supported by real time data)	22/03/2018	28/09/2018	SmPC	
IB/0052	B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	10/01/2018	n/a		
IB/0053	B.II.e.5.d - Change in pack size of the finished product - Change in the fill weight/fill volume of nonparenteral multi-dose (or single-dose, partial use) products	05/01/2018	n/a		
IB/0051	B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	20/11/2017	n/a		
IB/0050	B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	30/08/2017	n/a		
X/0046/G	This was an application for a group of variations. Annex I_2.(c) Change or addition of a new strength/potency Annex I_2.(d) Change or addition of a new	21/04/2017	06/07/2017	SmPC, Annex II, Labelling and PL	

	pharmaceutical form C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one Annex I_2.(c) Change or addition of a new strength/potency				
IA/0049/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites B.I.a.3.a - Change in batch size (including batch size ranges) of AS or intermediate - Up to 10-fold increase compared to the originally approved batch size B.I.a.3.b - Change in batch size (including batch size ranges) of AS or intermediate - Downscaling down to 10-fold B.I.a.3.b - Change in batch size (including batch size ranges) of AS or intermediate - Downscaling down to 10-fold	28/04/2017	n/a		
IB/0048	B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	12/09/2016	n/a		
IB/0047	B.II.f.1.b.1 - Stability of FP - Extension of the shelf life of the finished product - As packaged for sale (supported by real time data)	09/09/2016	06/07/2017	SmPC	
PSUSA/1934/ 201508	Periodic Safety Update EU Single assessment - maraviroc	17/03/2016	n/a		PRAC Recommendation - maintenance

II/0045/G	This was an application for a group of variations. 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.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	25/02/2016	n/a		
N/0044	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	27/11/2015	10/03/2016	PL	
WS/0645	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of section 4.6 of the SmPC to include the WHO guidelines on breastfeeding. The Package Leaflet has been updated accordingly. In addition, the WSA has taken the opportunity to promote consistency across products by updating where relevant (i.e. for Trizivir, Combivir, Lamivudine/Zidovudine ViiV and Triumeq), the pharmacokinetic statements in section 4.6 of the SmPC to reflect the most recently approved wording for the components abacavir and lamivudine (Kivixa EMEA/H/C/581/R/0051 and Epivir EMEA/H/C/107/II/0084). C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance	23/04/2015	10/03/2016	SmPC and PL	

	data				
II/0041	Update of sections 4.4 and 5.1 of the SmPC further to the 48-week time point results of Study A4001098 conducted to evaluate "the safety of Maraviroc in combination with other antiretroviral agents in HIV-1-infected subjects co-infected with hepatitis C and/or hepatitis B virus" (MEA 010.3). The MAH also took the opportunity to make minor editorial corrections in the SmPC and to bring the Package leaflet in line with the SmPC. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	26/03/2015	10/03/2016	SmPC and PL	Clinical data from study A4001098 suggest a similar incidence of grade 3 and 4 liver abnormalities with the use of maraviroc in combination with other retroviral agents in HIV patients co-infected with hepatitis B and/or C compared to placebo. Nevertheless, caution should be exercised when treating patients with hepatitis B and/or C virus co-infection.
IG/0438	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	16/05/2014	n/a		
WS/0544	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of section 4.4 of the SmPC with a revised wording on the risk of transmission as requested by the CHMP. The PL has been updated accordingly. In addition, minor corrections are made to translations and an editorial change is implemented in Trizivir PL. C.I.z - Changes (Safety/Efficacy) of Human and	25/04/2014	06/05/2015	SmPC and PL	The warnings in product information regarding the risk of transmission have been updated as requested by the CHMP in a class labelling request adopted in December 2013. Minor corrections are made to translations of Combivir SmPC in Danish and PL in Finnish and Slovenian, Celsentri SmPC and PL in Finnish and Hungarian, Telzir PL in Finnish, Tivicay SmPC in Dutch.

	Veterinary Medicinal Products - Other variation				
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.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method	11/04/2014	n/a		
II/0037	Submission of results of observational post authorisation safety studies conducted to evaluate the risk of non-AIDS malignancies and investigating also other events. These studies have been conducted as an additional pharmacovigilance activity required in the RMP. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	23/01/2014	n/a		
II/0034	Update of SmPC section 4.5 with information on interactions between maraviroc and ritonavir boosted elvitegravir. Furthermore, information on expected	18/12/2013	21/02/2014	SmPC and PL	One in vivo interaction study was submitted to evaluate the effect of maraviroc on ritonavir boosted elvitegravir and vice versa. The study showed that the PK of elvitegravir

	interactions with cobicistat has been included in SmPC sections 4.2 and 4.5. The PL has been updated in accordance. In addition, the statement on paediatric population in SmPC section 4.2 has been corrected. Furthermore, the text of the PL has been updated to bring it in line with information in the SmPC and to implement some editorial changes. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				and ritonavir was not affected by coadministration of maraviroc. In line with previous results obtained with ritonavir-boosted PIs, the Cmax and AUC of maraviroc was increased around 2- and 3-fold when co-administered with ritonavir boosted elvitegravir, therefore the observed impact on maraviroc was attributed mainly to ritonavir. Since according to the approved SmPC elvitegravir is always to be co-administered with ritonavir boosted protease inhibitor, the CHMP concluded that recommendations provided for coadministration with respective ritonavir boosted protease inhibitor should be followed. In addition, the CHMP requested to include recommendations regarding co-administration with recently approved medicinal product cobicistat (a potent CYP3A inhibitor).
II/0036	Update of SmPC section 5.1 with results from a retrospective re-analysis of efficacy at week 48 in subjects with only R5 tropic virus, confirmed by a more sensitive phenotypic tropism assay. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	24/10/2013	21/02/2014	SmPC	The MAH conducted a post hoc re-analysis of efficacy at week 48 in subjects with only R5 tropic virus, as confirmed by a more sensitive phenotypic tropism assay (Trofile-ES). A slight increase in percentage of patients with HIV-1 RNA < 50 copies/mL was seen in the maraviroc arm (48.2% vs. 45.5%), while the outcome in the placebo (optimised background therapy only) arm was not affected (16.3% vs. 16.7%).
II/0033	Update of SmPC section 4.8 with long term data from open label extensions of pivotal phase III studies. In addition, editorial changes are made in the SmPC section 5.1 and minor corrections of numerical data are implemented in table 6 of SmPC section 5.1.	24/10/2013	21/02/2014	SmPC	Data from open label observational extension phase (treatment duration up to 5 years) of pivotal studies showed that incidence of death, AIDS-defining events, hepatic failure, myocardial infarction/cardiac ischaemia, malignancies, rhabdomyolysis and other serious infectious events with maraviroc treatment was consistent with the incidence seen at earlier time-points in the studies.

	C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				
II/0035	Update of SmPC sections 4.2 and 4.5 - addition of information on drug-drug interactions with boceprevir and telaprevir, and inclusion of boceprevir and telaprevir as examples of potent CYP3A4 inhibitors requiring maraviroc dose reduction in patients with renal impairment. The Package Leaflet is updated in accordance. This variation is based on results of a study conducted as a post-authorisation measure. 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	21/02/2014	SmPC and PL	Data from a drug-drug interaction study between maraviroc and boceprevir or telaprevir indicted that coadministration with boceprevir or telaprevir increased the exposure of maraviroc 3.0 and 9.5 times, respectively. However, maraviroc did not affect the pharmacokinetics of boceprevir or telaprevir.
II/0032	Update of warnings on postural hypotension in SmPC section 4.4 and addition of information on cases of syncope caused by postural hypotension in SmPC section 4.8. The Package Leaflet has been updated in accordance. In addition, Product Information has been amended in line with latest QRD template and the list of local representatives has been updated 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	19/09/2013	21/02/2014	SmPC and PL	Previously conducted non-clinical studies were suggestive of a vasodilatory effect of maraviroc. In phase I studies postural hypotension (PH) was found to be a dose-limiting toxicity. In Phase IIb/III studies the rates of symptomatic postural events recorded as adverse events for both Celsentri and placebo arms were similar. However, a slightly higher frequency of PH related asymptomatic findings in treatment experienced population was observed in the maraviroc treatment arms (compared to placebo arms). The review of the marketing authorisation holder's safety database (data lock point 12th November 2012) identified 15 cases which described events of symptomatic postural hypotension in subjects with renal disease or additional risk factors. Consequentially, the information in

					the Product Information regarding the risk of postural hypotension has been updated recommending caution when using Celsentri in patients on concomitant medicinal products known to lower blood pressure, in patients with severe renal insufficiency and in patients who have risk factors for, or have a history of postural hypotension. In addition, possible increased risk of cardiovascular adverse events triggered by postural hypotension in patients with cardiovascular co-morbidities is described.
IB/0030	To include information on a class labelling for all antiretrovirals to revise section 4.4 and section 4.8 of the SmPC to include information regarding Autoimmune Disorders under Immune Reactivation Syndrome. The changes have also been reflected in the PL. 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	25/05/2013	21/02/2014	SmPC and PL	
IG/0295	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	29/04/2013	n/a		
II/0028	Update of section 4.5 of the SmPC with results from a pharmacokinetic interaction study with digoxin. 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	21/02/2014	SmPC	In an open-label, fixed sequence crossover interaction study between maraviroc (300 mg twice daily) and digoxin (single dose of 0.25 mg) in 12 healthy subjects the overall extent of exposure to digoxin following concomitant administration of maraviroc and digoxin was similar to that following administration of digoxin alone. The bounds of the

					90% CIs for the primary endpoint AUClast were completely contained within the established equivalence limits of 80% to 125%. The 90% CI for the Cmax ratios of test/reference were 83.80% to 129.18%. It was therefore concluded that maraviroc does not significantly affect AUClast, Cmax or Tmax of digoxin. The fact that the highest recommended maraviroc dose (in some co-administrations) of 600 mg twice daily has not been studied has been highlighted in the SmPC. The CHMP also concluded that the presented data do not exclude possibility of an effect of maraviroc on more sensitive P gp substrates (e.g. dabigatran etexilate).
II/0029	Update of section 4.5 of the SmPC with regard to the interaction between maraviroc and fosamprenavir, including a recommendation not to use this combination. SmPC section 4.2. has been updated accordingly. In addition, minor editorial changes have been made in the SmPC and 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	21/02/2013	21/02/2014	SmPC and PL	Data from two interaction studies investigating the effect of maraviroc on fosamprenavir/rtv and vice versa were presented. Both drugs were administered to steady state levels. The results obtained in the two studies were contradictory with regard to the effect of fosamprenavir/rtv on maraviroc: study A4001103 indicated increased maraviroc exposure, whereas the study COL112237 indicated reduced maraviroc exposure. Of note, results from study COL112237 were available only in the form of an abstract, and the assessment was therefore limited. Possible reasons for the different outcomes in the two studies were discussed but no obvious reason for the deviating results was found. In both studies the exposure of amprenavir, the active metabolite of fosamprenavir, decreased when co-administered with maraviroc. Considering that safety of maraviroc has been shown for maraviroc exposure of greater magnitude than in submitted studies, while risk for underexposure is regarded of a more serious concern, the CHMP concluded that the dosage for maraviroc should not be reduced and would have to be

					maintained at 300 mg BID when given with FPV/RTV. However, the reduction seen in the plasma levels for amprenavir when FPV/RTV is co-administered with MVC 300 mg BID (Cmin reduced by 36%) may be clinically relevant, therefore the CHMP supported not to recommend this combination.
II/0027	Update of the recommendations in case of an overdose in section 4.9 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	21/02/2013	21/02/2014	SmPC	The MAH initially proposed to remove reference to gastric lavage in the overdose section of the SmPC and to add a recommendation to contact National Poison centres. The advice to contact Poison centres was endorsed by the CHMP, but not the proposal to remove reference to gastric lavage, as it may be appropriate in at least some cases of severe overdosing.
II/0026	Inclusion in SmPC section 4.4 of a warning on reported severe skin and hypersensitivity reactions and update of the corresponding information in SmPC section 4.8. In addition, Annex II is being updated according to the latest QRD template version, minor editorial changes are implemented in SmPC and Labelling. Furthermore, the list of Local Representatives is being updated 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	21/02/2013	21/02/2014	SmPC, Annex II, Labelling and PL	A review of safety data in order to capture cases related to delayed hypersensitivity, with or without concomitant skin and/or liver reactions, was conducted by the MAH. Of the identified 161 reports (excluding 5 duplicates) 35 cases comprised features of delayed-type hypersensitivity reactions and were temporally related to initiation of treatment with maraviroc. Among those, 8 cases of Stevens-Johnson syndrome / toxic epidermal necrolysis, 4 cases of Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) and 4 cases of hepatic events that may meet the diagnostic criteria for DRESS were described. The frequency with which these events occur was found to be low, and in the vast majority of the reported cases it was concluded to be quite unlikely that the reaction was caused by maraviroc, but causal relationship in these potentially very serious cases cannot be excluded. Therefore, the SmPC has been updated accordingly with a warning in

					section 4.4 and an updated information in section 4.8.
R/0025	Renewal of the marketing authorisation.	24/05/2012	20/07/2012	SmPC, Annex II, Labelling and PL	Based on the CHMP review of the available information and on the basis of a re-evaluation of the benefit risk balance, the CHMP is 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 Celsentri continues to be favourable. The CHMP is of the opinion that the renewal can be granted with unlimited validity. Finally, the standard PSUR submission schedule apply and the next PSUR should cover the period 6 August 2011 - 5 August 2012 and is due no later than 60 days after DLP.
N/0024	The MAH took this opportunity to update the Package Leaflet to bring it in line with the change previously introduced in section 4.8 of the SmPC. In addition the MAH has updated the local representative contact details for Belgium and Luxemburg and has also made minor linguistic changes in the Package Leaflet for Spain to bring it in line with the English. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	16/03/2012	20/07/2012	PL	The MAH took this opportunity to update the PL to bring it in line with the change previously introduced in section 4.8 of the SmPC. In addition the MAH has updated the local representative contact details for Belgium and Luxemburg and has also made minor linguistic changes in the PL for Spain to bring it in line with the English.
IB/0023/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.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	06/12/2011	n/a		

II/0022	Update of sections 4.4 and 4.8 of the SmPC with adverse events of hepatotoxicity with allergic features. This change arises from the assessment of PSUR 5 and FUM 32.1. 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	20/10/2011	21/11/2011	SmPC	Further to the assessment of PSUR 5 and FUM 32.1 in which the MAH provided a comprehensive review of the available data with regard to the risk of hepatic disorders, the CHMP recommended a revision of the SmPC to reflect new available safety information. Overall, review of the available information from clinical studies and post-marketing surveillance does not establish that maraviroc causes serious hepatotoxicity. In nearly all the serious hepatic cases reported there have been other alternative causes for the events, and no cases have provided strong evidence for a causal association with maraviroc. Nevertheless, considering the cases in which patients have experienced hepatotoxicity in association with rash 2-3 weeks after starting maraviroc treatment, it is possible that maraviroc may be associated with a drug-induced hypersensitivity syndrome with prominent liver involvement. Therefore, sections 4.4 and 4.8 of the SmPC have been updated to reflect the occurrence of additional reports of hepatic failure with allergic features in the post-authorisation setting and clinical trials.
II/0018/G	This was an application for a group of variations. Grouped application to implement changes relating to the manufacturing process of maraviroc (active substance), including: - addition of an alternative manufacturing process for maraviroc, - minor change in the specification for maraviroc, - introduction of a new design space for the	23/06/2011	23/06/2011		

	alternative manufacturing process. B.I.a.2.b - Changes in the manufacturing process of the AS - Substantial change to the manufacturing process of the AS which may have a significant impact on the quality, safety or efficacy of the medicinal product B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method B.I.e.1.a - Design Space - Introduction of a new design space or extension of an approved design space for the AS - One unit operation in the manufacturing process of the AS including the resulting IPCs and/or test procedures				
IA/0020	B.II.a.1.a - Change or addition of imprints, bossing or other markings including replacement, or addition of inks used for product marking - Changes in imprints, bossing or other markings	25/03/2011	n/a	SmPC and PL	
IA/0019	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	28/02/2011	n/a		
II/0015	Update of the Detailed Description of the Pharmacovigilance System (DDPS) to ViiV Healthcare Ltd. The Annex II has been updated accordingly. In addition, editorial changes to the SmPC (sections 2,	18/11/2010	20/12/2010	SmPC, Annex II and PL	Update of the Detailed Description of the Pharmacovigilance System (DDPS) to ViiV Healthcare Ltd (version 2.0) dated September 2010

	4.4, 4.5, 4.8) and PL have been introduced. Details of the local representatives in Spain and Portugal have been updated. Translation errors in the Hungarian and the Latvian PI have been corrected. C.I.8.a - Introduction of a new Pharmacovigilance system - which has not been assessed by the relevant NCA/EMA for another product of the same MAH				
IA/0017	B.II.a.1.a - Change or addition of imprints, bossing or other markings including replacement, or addition of inks used for product marking - Changes in imprints, bossing or other markings	18/11/2010	n/a	SmPC and PL	
IA/0016	B.II.a.1.a - Change or addition of imprints, bossing or other markings including replacement, or addition of inks used for product marking - Changes in imprints, bossing or other markings	18/06/2010	n/a	SmPC and PL	
II/0010	To update sections 4.4, 4.5 and 4.8 of the SmPC with safety information coming from PSURs 2 and 3. Furthermore this procedure will align the Product Information annexes with the MAH Core Data Sheet. In addition the SmPC has been updated to reflect the latest amendments to the QRD template. Update of Summary of Product Characteristics and Package Leaflet	22/04/2010	02/06/2010	SmPC, Annex II and PL	After the assessment of the PSUR 2 and 3, the CHMP requested the update of the section 4.8 of the SPC regarding the hepatic failure and the Steven Johnson Syndrome (SJS). The safety profile of Celsentri has been summarised in the table 4 of the SPC and represents the broadest safety information available on Celsentri. Furthermore, this procedure will align the Product Information annexes with the MAH Core Data Sheet.
T/0014	Transfer of Marketing Authorisation	12/03/2010	05/05/2010	SmPC, Labelling and	

				PL	
II/0011	Extension of the shelf-life of Celsentri 150 mg and 300 mg film-coated tablets from 36 months to 48 months. Change(s) to shelf-life or storage conditions	18/02/2010	26/03/2010	SmPC	
II/0009	Update of Summary of Product Characteristics Update sections 4.2, 4.4 and 5.2 of the SPC to include information on the use of maraviroc in patients with renal impairment. These changes are further to the results of study A4001075 which fulfils one of the initial commitments made by the MAH. Update of Summary of Product Characteristics	18/02/2010	26/03/2010	SmPC	A study compared the pharmacokinetics of a single 300 mg dose of Celsentri in subjects with severe renal impairment (CLcr < 30 ml/min, n=6) and end-stage renal disease (ESRD) to healthy volunteers (n=6). Results show that dialysis had a minimal effect on exposure in subjects with ESRD. Exposures observed in subjects with severe renal impairment and ESRD were within the range observed in single Celsentri 300 mg dose studies in healthy volunteers with normal renal function. Therefore, no dose adjustment is necessary in patients with renal impairment receiving Celsentri without a potent CYP3A4 inhibitor. Dose adjustment is necessary in patients with renal impairment receiving Celsentri with potent CYP3A4 inhibitors. Therefore, this study in addition compared the pharmacokinetics of multiple dose Celsentri in combination with saquinavir/ritanovir 1000/100 mg twice a day (BID) (a potent CYP3A4 inhibitor) for 7 days in subjects with mild renal impairment to healthy volunteers. Subjects received 150 mg of Celsentri at different dose frequencies (healthy volunteers - every 12 hours; mild renal impairment - every 24 hours; moderate renal impairment - every 48 hours). Results showed that dosing frequencies of longer than 24 hours in subjects with renal impairment may result in inadequate exposures between 24-48 hours. Dosage

					adjustments were updated with these results. If coadministered with potent CYP3A4 inhibitors, e.g. saquinavir/ritonavir, Celsentri 150 mg should be administered every 24 hours in patients with moderate renal impairment. Simulations indicating that exposure would be sufficient supported the reduction of the dose when combining Celsentri with fosamprenavir/ritonavir from 300 mg BID to 150 mg BID in all subjects with renal impairment.
IA/0013	To change in the legal entity name from Godecke GmbH to Pfizer Manufacturing Deutschland GmbH of an approved manufacturing site for Celsentri finished product. A.5.a - Administrative change - Change in the name and/or address of a manufacturer responsible for batch release	05/03/2010	n/a	Annex II and PL	
IB/0012	B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate	26/02/2010	n/a		
II/0006	Update of section 4.4 and 5.1 of the SPC further to the results of study A4001026 in treatment-naïve patients. Section 6.6 is amended to add the recommended statement for disposal measures. Update of Summary of Product Characteristics and Package Leaflet	24/09/2009	05/11/2009	SmPC and PL	Please refer to the assessment report: Celsentri-H-811-II-06-AR.

II/0007	Update of the Detailed Description of the Pharmacovigilance System (DDPS) to version 2.0 in line with the Volume 9 of the Notice to Applicants. Update of DDPS (Pharmacovigilance)	25/06/2009	07/08/2009	Annex II	The Detailed Description of the Pharmacovigilance System (DDPS) has been updated (version 2.0) in order to reflect various organisational changes as well as the change of the global safety database. Consequently, Annex II has been updated using the standard text including the new version number of the agreed DDPS.
II/0005	Update of section 4.5 of the SPC to reflect data obtained from two interactions studies where maraviroc was administered with raltegravir, etravirine or etravirine+darunavir/ritonavir. Section 2 of the PL is amended accordingly. In addition, section 6 of the PL is updated as regards the contact details for the local representative in Ireland in the United Kingdom. Update of Summary of Product Characteristics and Package Leaflet	25/06/2009	07/08/2009	SmPC and PL	Study A4001082 investigated the effects of raltegravir on the pharmacokinetics of maraviroc in 17 healthy volunteers who completed this 15 day study. Results showed that, when in combination both drugs have a decreased exposure. However, both decreases are considered clinically insignificant. No dose adjustment is therefore foreseen. Study A4001041, a parallel group two period crossover study investigating the effects of etravirine or etravirine+darunavir+boosted ritonavir on the pharmacokinetics of maraviroc in healthy volunteers who completed this 20 day study. Results showed that etravirine+darunavir+boosted ritonavir increased maraviroc exposures. Considering that etravirine alone in combination with maraviroc causes a decrease in maraviroc exposure, it was agreed that the recommended dose adjustment for maraviroc when in co-administration with etravirine+darunavir+boosted ritonavir should follow the recommended regimen when in combination with boosted protease inhibitors (i.e 150 mg twice daily). However, this adjustment is not necessary when in combination with fosamprenavir/ritonavir. This data is reflected in section 4.5 of the SPC and in section 2 of the PL.

II/0008	Update of section 5.1 of the SPC regarding failure with CXCR4- using virus as requested by the CHMP following the assessment of FU2 012.1 in February 2009. Update of Summary of Product Characteristics	29/05/2009	07/07/2009	SmPC	Around two thirds of patients failing with maraviroc in the pivotal studies (studies A4001027 and A4001028 had CXCR4-virus present at failure (mostly mixed with CCRR5-virus: "dual-mixed tropism"), while the other third failed with CCR5-virus only (which most of the time was fully sensitive to maraviroc, indicating poor compliance as the cause of failure). All patients who failed with CXCR4-virus or dual-mixed tropism and who remained in study off maraviroc (n=36) were followed with regards to viral tropism. Thirty-three of 36 patients, with a follow-up time of more than 35 days reverted back to have CCR5-virus only, while 3 patients still showed CXCR4-virus. This information is reflected in section 5.1 of the SPC.
II/0004	Update of section 4.5 of the SPC to reflect the effect of maraviroc on P-glycoprotein (P-gp) as requested by the CHMP in November 2007. The Detailed Description of the Pharmacovigilance System (DDPS) is updated in line with the Volume 9 of the Notice to Applicants. The contact details of the local representative in Germany are updated in the PL. Update of DDPS (Pharmacovigilance) Update of Summary of Product Characteristics and Package Leaflet	25/09/2008	31/10/2008	SmPC, Annex II and PL	An in vitro study investigating the inhibition effect of maraviroc over P-gp has shown that maraviroc inhibits P-glycoprotein in vitro (IC50 of digoxin efflux was 183 ?M). Systemic effects on P-glycoprotein are however unlikely to be of relevance as this value is far greater than that of the average Cmax (0.3 µM following a 300 mg twice daily dose). However, concentrations obtained in the gut after oral administration could be much higher and therefore the SPC in section 4.5 was amended to refer that maraviroc could inhibit P-glycoprotein in the gut and may thus affect bioavailability of certain drugs. The DDPS has been updated to the format required by Volume 9 of the Notice to Applicants and to reflect organisational and procedural changes which occurred since the Marketing Authorisation approval. The telephone number of the local representative in Germany was updated in section 6 of the PL.

II/0002	Update of section 5.1 of the SPC regarding R5-failure with CCR-tropism virus, as requested in April 2008 by the CHMP further to the assessment of updated data on resistance and tropism from the pivotal studies A4001027 and A40001028. Update of Summary of Product Characteristics	25/09/2008	31/10/2008	SmPC	The 48 week data of studies A4001027 and A4001028 (treatment experienced, pivotal studies) showed that 58 patients randomised to maraviroc therapy had a protocol defined treatment failure with R5-virus only. 22/58 (38%) had virus at failure with reduced sensitivity to maraviroc, defined as < 95% MPI (maximal percentage inhibition) in the trofile assay, while the other 36 patients showed virus still susceptible (MPI >95%). Markers correlating to low compliance were identified in the later group of patients. In patients failing therapy with R5-virus only, maraviroc might be considered still active if the MPI value is ?95% (Trofile Phenosense assay). Mutations correlating to the V3-loop were seen in >80% of clones. No signature mutations correlating to maraviroc resistance were identified, implying that multiple genetic pathways to resistance may exist and that mutations may be virus-specific.
II/0003	The Marketing Authorisation Holder applied for an extension of shelf-life of the finished product from 2 to 3 years. Change(s) to shelf-life or storage conditions	25/09/2008	28/10/2008	SmPC	
N/0001	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	14/03/2008	n/a	PL	