EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

INTELENCE

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/1335/ 201809	Periodic Safety Update EU Single assessment - etravirine	11/04/2019	n/a		PRAC Recommendation - maintenance
II/0055	Update of sections 4.4 and 4.8 of the SmPC to include the information that a higher incidence of Stevens-Johnson Syndrome (SJS) has been observed in children compared to the incidence reported in adult clinical trials, as assessed in the TMC125-EPPICC study submitted according to Art. 46 procedure (no.	28/03/2019		SmPC and PL	In the final TMC125-EPPICC study report, a postmarketing retrospective cohort study aiming at substantiating the long-term safety profile of etravirine in HIV 1 infected children and adolescents receiving etravirine with other HIV 1 antiretrovirals (N = 182), Stevens-Johnson Syndrome was reported at a higher incidence (1%) than has been reported in adult clinical trials (<0.1%). Based on this section 4.4 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).

	EMA/H/C/000900/P46/052). The Package Leaflet is updated accordingly. In addition, the Marketing authorisation holder (MAH) took the opportunity to make an amendment in section 4.2 of the SmPC by replacing the word “tablet” with “dose” in the missed dose information. The Package Leaflet is updated accordingly. Moreover, section 2 of the SmPC has been updated to include information on the sodium excipient as per the revised Annex to the European Commission guideline on ‘Excipients in the labelling and package leaflet of medicinal products for human use’. The Package Leaflet is updated in accordance. Furthermore, the list of local representatives have been updated in the Package Leaflet in line with the latest QRD template version 10.0. 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				4.8 of the SmPC are being updated.
IA/0056/G	This was an application for a group of variations. B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.III.2.b - Change to comply with Ph. Eur. or with	21/03/2019	n/a		

	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				
IG/0980	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	24/10/2018		SmPC and PL	
R/0052	Renewal of the marketing authorisation.	28/06/2018	23/08/2018	SmPC and PL	Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of INTELENCE in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity. Etravirine is excreted in human milk. As a general rule, it is recommended that mothers infected by HIV do not breastfeed their babies under any circumstances in order to avoid transmission of HIV.
PSUSA/1335/ 201709	Periodic Safety Update EU Single assessment - etravirine	12/04/2018	n/a		PRAC Recommendation - maintenance
II/0050	Update of sections 4.3, 4.4 and 4.5 of the SmPC to include additions to the drug-drug interaction (DDI) information of etravirine with hepatitis C virus (HCV) direct-acting antivirals (DAAs) elbasvir/grazoprevir, daclastavir and simeprevir and human immunodeficiency virus (HIV) protease inhibitors (PIs) atazanavir/cobicistat and darunavir/cobicistat, following the same changes in medicinal products containing these active substances. Section 4.9 of the SmPC is also updated with regard to treatment of etravirine	13/07/2017	30/07/2018	SmPC, Labelling and PL	

	overdose. In addition, the Marketing Authorisation Holder (MAH) took the opportunity to introduce minor editorial changes, to align the PL with SmPC regarding co-administration of etravirine with anti-HIV medicines efavirenz, nevirapine, rilpivirine, indinavir, nelfinavir, to update the list of local representative for the Netherlands in the PL and to align the PI with the latest the QRD template (version 10.0). C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
PSUSA/1335/ 201609	Periodic Safety Update EU Single assessment - etravirine	06/04/2017	n/a		PRAC Recommendation - maintenance
IA/0049/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.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release) 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	05/04/2017	n/a		

	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				
IB/0047	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	02/09/2016	n/a		
IA/0046/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites 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	08/07/2016	n/a		
N/0045	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	15/09/2016	PL	
PSUSA/1335/ 201509	Periodic Safety Update EU Single assessment - etravirine	14/04/2016	n/a		PRAC Recommendation - maintenance
WS/0872	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.	28/01/2016	15/09/2016	SmPC and PL	

	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation				
II/0042	Update of sections 4.2, 4.4, 5.1 and 5.2 of the SmPC in order to update the safety information of the TMC114HIV3015 study. In addition, the Marketing authorisation holder (MAH) took the opportunity to include information on the removal of gastric lavage in 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	24/09/2015	15/09/2016	SmPC	Update of sections 4.2, 4.4, 5.1 and 5.2 of the SmPC in order to update the safety information of the TMC114HIV3015 study. In addition, the Marketing authorisation holder (MAH) took the opportunity to include information on the removal of gastric lavage in section 4.9 of the SmPC.
PSUSA/1335/ 201409	Periodic Safety Update EU Single assessment - etravirine	10/04/2015	n/a		PRAC Recommendation - maintenance
IG/0526/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	04/03/2015	26/03/2015	Annex II and PL	
II/0039	Submission of the Clinical Study Report of study TMC125IFD3002 including data to fulfil element 1 of REC 043 (interaction data between etravirine and lopinavir/ritonavir in HIV infected patients). C.I.13 - Other variations not specifically covered	26/02/2015	n/a		

	elsewhere in this Annex which involve the submission of studies to the competent authority				
PSUV/0038	Periodic Safety Update	09/10/2014	n/a		PRAC Recommendation - maintenance
II/0036	Update of section 4.5 of the SmPC with information on interactions between etravirine (without or with ritonavir boosted darunavir or lopinavir) and dolutegravir. Furthermore, the PI is being brought in line with the latest QRD template version 9. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	22/05/2014	26/03/2015	SmPC, Annex II and PL	The drug interactions between etravirine (ETR) and dolutegravir (DTG) were investigated in an open-label, 2-period, crossover study in 16 healthy adult subjects. Dolutegravir did not appear to affect the PK of etravirine. Etravirine decreased plasma DTG concentration, which may result in loss of virologic response and possible resistance to dolutegravir. Dolutegravir should not be used with etravirine, as mentioned in the Tivicay (dolutegravir) SmPC. The drug interactions between ETR with lopinavir (LPV)/ritonavir (rtv) and DTG, and between ETR with darunavir (DRV)/rtv and DTG were investigated in a randomized, open-label, crossover study in 17 healthy adult subjects. Coadministration of ETR and LPV/rtv had no effect on the DTG AUCmin and Cmax and resulted in approximately 28% increase in Cmin at steady state. Coadministration of ETR and DRV/rtv resulted in decreased DTG exposures, with a more prominent effect on Cmin (37% reduction) than on AUC24h (25% reduction) and Cmax (12% reduction). Therefore, ETR can be coadministered with DTG and LPV/rtv, and with DTG and DRV/rtv without dose adjustment. The combination of ETR with DTG and another boosted PI, atazanavir/rtv, is anticipated to give a similar effect, and is therefore also allowed without dose adjustment.
IB/0037	B.II.f.1.b.2 - Stability of FP - Extension of the	25/04/2014	26/03/2015	SmPC	

	shelf life of the finished product - After first opening (supported by real time data)				
PSUV/0034	Periodic Safety Update	10/04/2014	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	26/03/2015	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.
PSUV/0033	Periodic Safety Update	24/10/2013	08/01/2014	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUV/0033.
II/0031	Submission of results of the final remaining specific obligation for the Conditional Marketing Authorisation and granting of a Marketing Authorisation not subject to specific obligations.	19/09/2013	20/11/2013	SmPC, Annex II and PL	The MAH submitted results of the last outstanding Specific Obligation – a retrospective observational cohort study including 1115 subjects treated by etravirine in combination with a protease inhibitor. The different efficacy results

	SmPC, Annex II and PL have been updated accordingly. In addition, list of local representatives in the PL has been updated. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation				regardless of the statistical method employed (with or without adjustment for confounding factors), the efficacy endpoint (virologic response observed or M=F, changes in viral load), or the baseline characteristics (viral load, HIV-1 subtype, virologic resistance status) did not show significant differences between subjects treated by etravirine in combination with daruvinavir/ritonavir (n=999) and those treated by etravirine in combination with protease inhibitors other than darunavir/ritonavir (n=116). The CHMP concluded that Specific Obligations for the Conditional Marketing Authorisation, as imposed at the time of initial authorisation and subsequently modified, have been fulfilled and therefore recommended granting of a Marketing Authorisation not subject to specific obligations.
IG/0341	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	31/07/2013	n/a		
IB/0030	B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	29/07/2013	n/a		
R/0028	Renewal of the marketing authorisation.	25/04/2013	21/06/2013		The CHMP, having reviewed the available information on the status of the fulfilment of Specific Obligations and having confirmed the positive benefit risk balance, is of the opinion that the quality, safety and efficacy of this medicinal product continue to be adequately and sufficiently demonstrated and therefore recommends the renewal of the conditional Marketing Authorisation for Intelence, subject to the Specific Obligations and Conditions as laid down in Annex II to the Marketing Authorisation.

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	01/07/2013	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/0024/G	This was an application for a group of variations. Grouping of two type II variations to update section 4.5 of the SmPC with information on drug interactions with artemether/lumefantrine and telaprevir. The PL is updated accordingly. In addition, editorial changes have been made in the interaction table in SmPC section 4.5 and the list of local representatives in the PL has been revised to amend contact details for the representative of Cyprus.	15/11/2012	06/03/2013	SmPC and PL	Two interaction studies were submitted, addressing the combination of etravirine with telaprevir and artemether/lumefantrine respectively. Co-administration of telaprevir with etravirine in healthy subjects was found to have no relevant effect on the pharmacokinetics of etravirine compared with administration of etravirine alone. In the combination the Cmin, Cmax, and AUC8h of telaprevir were reduced by 25%, 10%, and 16%, respectively (compared to administration of telaprevir alone) but these changes were not considered to be of clinical relevance.

	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				With artemether/lumefantrine, a significant decrease in the pharmacokinetics of artemether and dihydroatemisine (its active metabolite) were observed. Lumefantrine Cmax and Cmin did not significantly change whereas its AUC fell outside the predefined limits of [0,8-1.25]. Etravirine pharmacokinetics did not significantly change in this combination. It is concluded that there is a risk of antimalarial treatment failure when etravirine is combined with artemether/lumefantrine, which is reflected in the SmPC. The data presented in this variation does not affect the benefit/risk balance of etravirine.
X/0018/G	This was an application for a group of variations. Line Extension of the Marketing Authorisation concerns a new strength (25 mg). Update the section 4.1 of the SmPC for the existing 100mg and 200mg tablet with the new paediatric indication (children from the age of 6 years) and introduce consequential changes to the Annexes I, II.C, IIIa and IIIb. Changes to the product information were introduced in line with the QRD template. Annex I_2.(c) Change or addition of a new strength/potency C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	15/11/2012	06/03/2013	SmPC, Annex II, Labelling and PL	Please refer to Assessment Report: Intelence-H-C-900-X-18-G-AR
II/0027	Update of section 4.5 of the SmPC in order to	21/02/2013	21/06/2013	SmPC and	No clinical data was submitted. It is known that rilpivirine is

	include rilpivirine as an example of non-nucleoside reverse transcriptase inhibitors that are not recommended to be co-administered with etravirine. In addition, the Annex II is being brought in line with the latest QRD 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			Annex II	primarily metabolised by CYP3A and etravirine is a weak inducer of this enzyme. Therefore, there is a risk of decrease in rilpivirine plasma concentration and consequentially of a loss of its therapeutic effect. In addition, pharmacodynamic and safety considerations lead to discourage the co-administration of two NNRTIs. Furthermore, etravirine and rilpivirine are not indicated for the same HIV-infected populations. The CHMP therefore supported MAH's proposal to include rilpivirine as an example of non-nucleoside reverse transcriptase inhibitors that are not recommended to be co-administered with etravirine.
IG/0213	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	28/08/2012	n/a		
R/0023	Renewal of the marketing authorisation.	24/05/2012	20/07/2012	Annex II	The CHMP, having reviewed the available information on the status of the fulfilment of Specific Obligations and having confirmed the positive benefit risk balance, is of the opinion that the quality, safety and efficacy of this medicinal product continue to be adequately and sufficiently demonstrated and therefore recommends the renewal of the conditional MA for Intelence, subject to the Specific Obligations and Conditions as laid down in Annex II to the Opinion.
IA/0025	A.7 - Administrative change - Deletion of manufacturing sites	13/07/2012	n/a		
II/0020	The MAH proposed the update of section update of section 4.6 of the SmPC with the latest information available from the Antiretroviral Pregnancy Registry. In addition, the MAH took the opportunity to update the list of local	16/02/2012	19/03/2012	SmPC and PL	Based on animal data with Intelence the malformative risk is unlikely in humans. The clinical data with Intelence (including the latest information available from the Antiretroviral Pregnancy Registry) do not raise safety concern but are very limited.

	representatives in the Package Leaflet (Spain, Latvia, Cyprus, Slovak Republic, and Romania). C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				As a general rule for HIV medicines, when deciding to use antiretroviral agents for the treatment of HIV infection in pregnant women and consequently for reducing the risk of HIV vertical transmission to the newborn, the animal data as well as the clinical experience in pregnant women should be taken into account in order to characterise the safety for the fetus. In addition, it is recommended that mothers infected by HIV do not breast-feed their babies, under any circumstances in order to avoid transmission of HIV.
IA/0022	B.II.b.2.a - Change to batch release arrangements and quality control testing of the FP - Replacement or addition of a site where batch control/testing takes place	24/02/2012	n/a		
IB/0021	B.II.b.2.a - Change to batch release arrangements and quality control testing of the FP - Replacement or addition of a site where batch control/testing takes place	12/01/2012	n/a		
IA/0019	B.II.b.2.a - Change to batch release arrangements and quality control testing of the FP - Replacement or addition of a site where batch control/testing takes place	16/12/2011	n/a		
X/0012	Addition of 200 mg tablet Annex I_2.(c) Change or addition of a new strength/potency	22/09/2011	24/11/2011	SmPC, Annex II, Labelling and PL	
II/0014	Update of section 4.5 of the SmPC to add a new	21/07/2011	24/08/2011	SmPC and PL	In vitro data show that etravirine has inhibitory properties on

	drug drug interaction with clopidrogel. The PL is updated accordingly. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				CYP2C19. It is therefore possible that etravirine may inhibit the metabolism of clopidogrel to its active metabolite by such inhibition of CYP2C19 in vivo. The clinical relevance of this interaction has not been demonstrated. As a precaution it is recommended that concomitant use of etravirine and clopidogrel should be discouraged
R/0015	Renewal of the marketing authorisation.	19/05/2011	20/07/2011	SmPC and Annex II	Based on the CHMP review of the available information on the status of the fulfilment of Specific Obligations and having confirmed the positive 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 recommends the renewal of the conditional MA for Intelence, subject to the Specific Obligations and Conditions as laid down in Annex II to the Opinion and reflected in the MAH's Letter of Undertaking.
IG/0090/G	This was an application for a group of variations. C.I.9.c - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the back-up procedure of the QPPV C.I.9.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	08/07/2011	n/a		

IG/0023/G	This was an application for a group of variations. 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 C.I.9.e - Changes to an existing pharmacovigilance system as described in the DDPS - Changes in the major contractual arrangements with other persons or organisations involved in the fulfilment of pharmacovigilance obligations and described in the DD	21/09/2010	n/a	Annex II	
IA/0011	C.I.9.c - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the back-up procedure of the QPPV	21/07/2010	n/a	Annex II	To update the Detailed Description of the Pharmacovigilance System (DDPS) to version 5.1, to include a change of the backup procedure of the Qualified Person for Pharmacovigilance (QPPV). As a consequence, Annex II of the current Product Information has been updated with the new version number of the agreed DDPS.
R/0009	Renewal of the marketing authorisation.	22/04/2010	02/07/2010		Based on the CHMP review of the available information on the status of the fulfilment of Specific Obligations and having confirmed the positive 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 recommends the renewal of the conditional MA for Intelence, subject to the Specific Obligations and Conditions as laid down in Annex II to the Opinion and reflected in the MAH's Letter of Undertaking.

II/0005	To update section 4.5 of the SmPC to reflect the results of the interaction study between etravirine and voriconazole/fluconazole fulfilling follow-up measure 08. The MAH took the opportunity of this variation to update the SmPC and PL with the new EMA website Update of Summary of Product Characteristics and Package Leaflet	18/03/2010	29/04/2010	SmPC and PL	The MAH has conducted a complete drug-drug interaction study to investigate the two-way interactions between etravirine and fluconazole and etravirine and voriconazole. Regarding the interaction of etravirine with fluconazole as expected due to the main excretion of fluconazole on unchanged form by urinary way, no effect has been observed on fluconazole pharmacokinetics in case of co-administration with etravirine. On the contrary, fluconazole increased etravirine PK parameters by about a 2-fold factor. Since no safety signal emerged from this interaction study or from other clinical safety data such an increase in etravirine exposure is not expected to alter the safety profile of etravirine in HIV-infected patients receiving fluconazole in combination with etravirine. Therefore, etravirine and fluconazole can be used without dose adjustments. Regarding the interaction of etravirine with voriconazole voriconazole increased the etravirine PK parameters, but to a lesser extent than did fluconazole (less than 50% with voriconazole compared to about 100% with fluconazole). When analysing the effect of etravirine co-administration on voriconazole PK parameters the situation is more complicated because of the dependence of voriconazole metabolism on CYP2C19 genotype. As expected, patients presenting a CYP2C19*2 allele (i.e. intermediate or poor metabolisers) presented higher voriconazole PK parameters than patients not presenting this allele. However, and as a reassuring finding, in these patients (who can be considered as the worst-case scenario), etravirine decreased the voriconazole PK parameters. On the contrary, in extensive metabolisers, etravirine increases the voriconazole PK parameters (AUC +50%). Overall, in the whole population, in the presence of etravirine, Cmin and AUC12h of voriconazole

					were increased by 23% and 14%, respectively, while Cmax of voriconazole was decreased by 5%, when combined with etravirine. Therefore etravirine and voriconazole can be used without dose adjustments.
II/0008	Update of the DDPS (version 5.0) to include non-QPPV related changes to the DDPS performed since the last approved version. Consequently, Annex II has been updated using the standard text including the new version number of the DDPS. Update of DDPS (Pharmacovigilance)	18/02/2010	30/03/2010	Annex II	With this variation the MAH submitted a new version of the DDPS (version 5.0) in accordance with the current Pharmacovigilance guideline. After assessing the documentation the CHMP concluded that the submitted DDPS contained all required elements. Consequently, Annex II has been updated with the new version number of the agreed DDPS
IA/0010	To replace a manufacturing site where testing takes place B.II.b.2.a - Change to batch release arrangements and quality control testing of the FP - Replacement or addition of a site where batch control/testing takes place	04/03/2010	n/a		To replace a manufacturing site where testing takes place
II/0004	Update section 4.5 of the SPC to reflect the results of the interaction study between etravirine and lopinavir/ritonavir in healthy volunteers. This study fulfils one of the initial commitments made as follow-up measure. The MAH took the opportunity of this variation to update the contact details of the local representative in Greece in section 6 of the PL. Furthermore, the MAH proposed administrative changes throughout the SPC, as relevant. In addition the PL was revised to	22/10/2009	26/11/2009	SmPC and PL	By the time of the marketing authorisation application, an interaction study was performed between etravirine and lopinavir/ritonavir capsules. The study showed an increase in etravirine pharmacokinetic parameters and a decrease in the lopinavir PK parameters. The interaction was judged as not-clinically relevant, as described in the SPC up to now. Additionally, the MAH had planned, as a post-authorisation commitment, to perform a new interaction data with the current formulations (tablet formulation of lopinavir/ritonavir and the commercial formulation of etravirine). Results of the

	be in line with the SPC changes endorsed during the variation II/06. Update of Summary of Product Characteristics and Package Leaflet				study confirmed no clinically relevant effects of etravirine on either lopinavir or ritonavir pharmacokinetics. This new interaction study showed a decrease in etravirine PK parameters in the presence of lopinavir/ritonavir, compared to treatment with etravirine alone contrary to what was observed in previous interaction study with lopinavir/ritonavir capsules. The differences seen could be explained by differences in trial design and formulation. Since this final study included the current formulations of etravirine and lopinavir/ritonavir these results are consider more relevant. Overall the pharmacokinetic interactions observed between etravirine and lopinavir/ritonavir were not considered clinically relevant and the CHMP recommends no dose adjustment when etravirine is co-administered with lopinavir/ritonavir. This study confirmed that co-administration of etravirine with lopinavir/ritonavir was safe and well tolerated.
II/0007	Update of section 4.5 of the SPC to include information on dosing recommendations when etravirine is co-administered with rifabutin with an associated boosted protease inhibitor as agreed by the CHMP in July 2009 following evaluation of a follow up measure. Update of Summary of Product Characteristics	22/10/2009	12/11/2009	SmPC	The interaction between etravirine and rifabutin was evaluated in a trial during the marketing authorisation and is described in the SPC. Since etravirine should be administered in combination with a boosted protease inhibitor a thorough assessment of each potential interaction between etravirine with both a ritonavir-boosted protease inhibitor and rifabutin was performed. The CHMP concluded that the SPC should be updated to inform that a decrease in etravirine exposure is expected and a close monitoring for virologic response should be recommended. An absence or a moderate increase in rifabutin exposure is expected whereas a high increase in the 25-O-desacetylrifabutin (a metabolite of rifabutin) exposure is predicted. Therefore, a close monitoring for

					rifabutin-associated adverse reactions should be recommended and reference should be made to the corresponding protease inhibitor for dose adjustment.
II/0006	Update of sections 4.4 and 4.8 of the SPC to reflect cases of toxic epidermal necrolysis and other hypersensitivity reactions reported with etravirine treatment. Sections 2 and 4 of the PL have been updated accordingly. Update of Summary of Product Characteristics and Package Leaflet	24/09/2009	04/11/2009	SmPC and PL	Further to cases of severe hypersensitivity reactions reported during treatment with etravirine, including two cases of toxic epidermal necrolysis with one fatal outcome, the SPC and PL for Intelence was amended and a Direct Healthcare Professional Communication letter was issued to advice on this new safety information.
R/0003	Renewal of the marketing authorisation.	29/05/2009	03/08/2009	Annex II	Based on the CHMP review of the available information on the status of the fulfilment of Specific Obligations and having confirmed the positive 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 recommends the renewal of the conditional MA for Intelence, subject to the Specific Obligations and Conditions as laid down in Annex II to the Opinion and reflected in the MAH's Letter of Undertaking.
II/0002	Update of sections 4.1, 4.4, 4.5, 4.8 and 5.1 of the SPC and section 4 of the PL to reflect the results of 48 week pooled data from the pivotal DUET-1 and DUET-2 studies. The contact details of the local representatives in Malta, Norway, Finland and UK are updated in section 6 of the PL. Update of Summary of Product Characteristics and Package Leaflet	19/03/2009	23/04/2009	SmPC and PL	The pooled data from the 48 week data from the pivotal DUET-1 and DUET-2 studies confirm the efficacy and safety results seen at time of the initial Marketing Authorisation (MA) for Intelence. The results derived from subgroups of very limited sample size (non clade B, hepatitis co-infection) do not allow a clear conclusion despite the pooling data. No new safety finding has been observed in the phase IIb/III pooled safety analysis which included the DUET studies. The safety profile of etravirine was similar to that seen in the

					pooled DUET analysis, except for the absence of the gender difference for rash at 48 weeks of treatment. However, the warning is still maintained in section 4.4 of the SPC since at this stage further data is awaited to further substantiate this observation. The relevant sections of the SPC and PL are updated to reflect these data.
II/0001	Update of section 5.3 of the SPC to reflect results of carcinogenicity studies in mice and rats. Update of Summary of Product Characteristics	19/03/2009	23/04/2009	SmPC	The carcinogenicity studies performed in mice and rats showed that etravirine is not carcinogenic in rats and male mice. However, a higher incidence of hepatocellular adenomas and carcinomas were seen in female mice. This hepatocellular finding is generally considered to be rodent specific and of limited relevance to humans. This information is reflected in section 5.3 of the SPC.