Fuzeon

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
N/0064	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	15/03/2023		PL	
IB/0063	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	22/11/2022		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).

				PL	
IA/0062	A.7 - Administrative change - Deletion of manufacturing sites	18/07/2022	n/a		
N/0061	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	04/11/2021		PL	
PSUSA/1217/ 202103	Periodic Safety Update EU Single assessment - enfuvirtide	28/10/2021	n/a		PRAC Recommendation - maintenance
N/0060	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	10/08/2021		PL	
IA/0058	A.7 - Administrative change - Deletion of manufacturing sites	21/10/2020	n/a		
IA/0057/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites	10/10/2019	n/a		
IB/0056	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	27/08/2019	n/a		
IB/0055	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	12/04/2019	n/a		

IA/0054/G	This was an application for a group of variations. 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 B.II.d.2.b - Change in test procedure for the finished product - Deletion of a test procedure if an alternative method is already authorised	09/01/2019	n/a		
IAIN/0053	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	11/10/2018	04/10/2019	SmPC	
II/0051/G	This was an application for a group of variations. B.I.b.1.f - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Change outside the approved specifications limits range for the AS B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure 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	27/09/2018	04/10/2019		

	starting material/reagent/intermediate - Minor changes to an approved test procedure B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits B.II.d.1.i - Change in the specification parameters and/or limits of the finished product - Ph. Eur. 2.9.40 uniformity of dosage units is introduced to replace the currently registered method, either Ph. Eur. 2.9.5 or Ph. Eur. 2.9.6 B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation B.II.d.2.a - Change in test procedure for the finished product - 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				
N/0052	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	09/08/2018	04/10/2019	PL	

T/0050	Transfer of Marketing Authorisation	20/02/2018	06/04/2018	SmPC, Labelling and PL	
PSUSA/1217/ 201603	Periodic Safety Update EU Single assessment - enfuvirtide	29/09/2016	n/a		PRAC Recommendation - maintenance
IA/0049	A.7 - Administrative change - Deletion of manufacturing sites	15/09/2016	n/a		
N/0048	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	09/08/2016	06/04/2018	Labelling	
PSUSA/1217/ 201503	Periodic Safety Update EU Single assessment - enfuvirtide	22/10/2015	16/12/2015	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/1217/201503.
IG/0573	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	01/07/2015	n/a		
IG/0497	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	18/11/2014	n/a		
PSUV/0042	Periodic Safety Update	09/10/2014	n/a		PRAC Recommendation - maintenance
IB/0043	B.II.b.1.e - Replacement or addition of a manufacturing site for the FP - Site where any	05/08/2014	n/a		

	manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non-sterile medicinal products				
II/0041	Update of section 4.8 of SmPC in line with the latest QRD template. PL has been updated accordingly. In addition, the warnings on the risk of transmission in SmPC section 4.4 and PL have been updated in line with class labelling request by the CHMP. Furthermore, the PL has been updated in line with the results of user testing, previously adopted recommendations for missed doses are included also in SmPC section 4.2 and the list of local representatives in the PL has been revised. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	20/03/2014	04/07/2014	SmPC and PL	SmPC section 4.8 has been updated to align with the format in the latest QRD template, without changes to the content of the safety information presented. In addition, the Package Leaflet has been revised based on results of readability testing and comments raised by the CHMP.
IB/0039/G	This was an application for a group of variations. B.II.e.5.b - Change in pack size of the finished product - Deletion of a pack size(s) C.I.7.a - Deletion of - a pharmaceutical form	14/06/2013	04/07/2014	SmPC, Annex II, Labelling and PL	
IB/0038	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	28/05/2013	04/07/2014	SmPC and PL	

IA/0040	A.7 - Administrative change - Deletion of manufacturing sites	23/04/2013	n/a		
IG/0228	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	23/11/2012	n/a		
N/0035	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	29/10/2012	04/07/2014	PL	
IG/0176	A.4 - Administrative change - Change in the name and/or address of a manufacturer or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS	25/06/2012	n/a		
IA/0033	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	01/06/2012	n/a		
II/0031	Update of Summary of Product Characteristics and Package Leaflet	18/03/2010	27/04/2010	SmPC and PL	
IB/0030	IB_42_a_01_Change in shelf-life of finished product - as packaged for sale	22/12/2009	n/a	SmPC	
IB/0029	IB_17_a_Change in re-test period of the active substance	12/02/2009	n/a		
IB/0028	IB_10_Minor change in the manufacturing process of the active substance	06/02/2009	n/a		

IA/0027	IA_09_Deletion of manufacturing site	21/07/2008	n/a		
R/0026	Renewal of the marketing authorisation.	24/04/2008	08/07/2008	SmPC, Annex II, Labelling and PL	
II/0025	Change in the manufacturer of the finished product. Quality changes	13/12/2007	18/12/2007		
II/0024	Update of Summary of Product Characteristics and Package Leaflet To update section 5.2 of the SPC with information on enfuvirtide levels in the cerebrospinal fluid, following the CHMP request on 25 January 2007. Furthermore, the MAH took the opportunity of this variation to replace two images in the PL to better illustrate the handling of the protective cap of the syringes. Update of Summary of Product Characteristics and Package Leaflet	20/09/2007	30/10/2007	SmPC and PL	An investigator-initiated study evaluated the pharmacokinetics of enfuvirtide in the cerebrospinal fluid (CSF) of four HIV-infected patients. The results showed that the penetration of enfuvirtide in the CSF is negligible. This information has been included in the SPC.
S/0023	Annual re-assessment.	19/07/2007	02/10/2007	Annex II	
II/0022	Update of sections 4.2, 4.4 and 5.2 of the SPC with additional data in patients with reduced renal function in line with the CHMP conclusion in assessment of FUM 098. Update of Summary of Product Characteristics	19/07/2007	30/08/2007	SmPC	Following submission of a study to investigate Pharmacokinetics of Enfuvirtide in HIV-1 infected subjects with renal impairment, it was concluded that the effect of severe renal impairment on enfuvirtide pharmacokinetics is limited, although few subjects were included in the study. The study did not reveal any safety concerns. Compared to historical data, the exposure obtained in this study is

					similar to earlier study results. The small increase in exposure in patients with severe renal impairment or patients undergoing haemodialysis does not require dose adjustment. The information from this study on patients with reduced renal function has been included in the SPC.
II/0020	Quality changes	21/06/2007	22/06/2007		
IA/0021	IA_05_Change in the name and/or address of a manufacturer of the finished product	18/04/2007	n/a	Annex II and PL	
II/0019	Update of section 4.4 and section 4.8 of the SPC and section 2 of the PL to implement the class labelling text on osteonecrosis, agreed by the CHMP in September 2006. In addition the MAH completed the list of local representatives in the PL to include the two new EU Member States (Bulgaria and Romania) according to the latest EMEA/QRD template. Update of Summary of Product Characteristics and Package Leaflet	14/12/2006	24/01/2007	SmPC and PL	Cases of osteonecrosis (death of the bone tissue resulting from an insufficient blood supply) have been reported in HIV-infected patients since the end of the 80's. Although the cause of this disease could be due to multi factors (including the use of corticosteroids, alcohol consumption, severe immunosuppression, higher body mass index) it has occurred specially in patients with HIV advanced disease and/or in patients with long term use of combination antiretroviral therapy (CART). Further to the review of all available data the CHMP agreed that this information should now be included in the SPC and PL of all antiretroviral medicinal products. Patients should be warned to seek medical advice in case they experience joint stiffness, aches and pain especially of the hip, knee and shoulder or if they experienced any difficulty in movement.
II/0017	Update of Summary of Product Characteristics, Annex II, Labelling and Package Leaflet To update sections 4.4 and 5.3 of the SPC as requested by CHMP following the evaluation of the	21/09/2006	24/10/2006	SmPC, Annex II, Labelling and PL	The MAH has submitted this variation in order to amend section 4.4 and 5.3 of the SPC as requested by CHMP following the evaluation of the Specific Obligation 1 concerning the immunotoxic potential of enfuvirtide observed in animal models. Animal studies have shown that

	Specific Obligation 1 concerning the immunotoxic potential of enfuvirtide . Furthermore, the MAH updated the product information according to the QRD template version 7. Update of Summary of Product Characteristics, Labelling and Package Leaflet				enfuvirtide may impair some immune functions.
S/0018	Annual re-assessment.	27/07/2006	21/09/2006	Annex II	
IA/0015	IA_01_Change in the name and/or address of the marketing authorisation holder	14/12/2005	n/a	SmPC, Labelling and PL	
IA/0014	IA_43_a_01_ Add./replacement/del. of measuring or administration device - addition or replacement	14/12/2005	n/a	PL	
IA/0016	IA_09_Deletion of manufacturing site	09/12/2005	n/a		
S/0013	Annual re-assessment.	28/07/2005	05/10/2005	Annex II	The CHMP reviewed the evidence of compliance with the specific obligations (SOBs) and reassessed the benefit- risk profile of the medicinal product. Some SOBs and follow-up measures remain unresolved. Therefore the CHMP agreed that the Marketing Authorisation remains under exceptional circumstances.
II/0012	Quality changes	17/02/2005	11/04/2005	SmPC, Labelling and PL	
II/0009	Quality changes	16/03/2005	22/03/2005		

II/0008	Change(s) to the test method(s) and/or specifications for the active substance Change(s) to the test method(s) and/or specifications for the finished product	16/03/2005	20/03/2005		
II/0011	Update of Summary of Product Characteristics and Package Leaflet	18/11/2004	17/12/2004	SmPC and PL	In patients treated with any type of combination antiretroviral therapy (CART), an inflammatory response to indolent or residual opportunistic infections may occur, when the immune system responds to treatment. In most cases, the inflammatory reactions towards the opportunistic pathogens in question cannot be foreseen since the opportunistic infection has not yet been detected/ diagnosed. if diagnosed prior to institution of CART, the treatment against the opportunistic infection (OI) is usually given priority. In particular, this is true for the complications most feared in this context; CMV-retinitis, generalised mycobacterial infectionsand Pneumocystis carinii pneumonia. An additional reason for treating the OI and the HIV-infection sequentially, is the great risk of adverse events (toxicity or lack of effect) due to drug interactions. in conclusion, in most cases, the clinical consequences of the awakening immune system in patients starting ART cannot be prevented. therefore, early recognition and diagnosis of these inflammatory reactions are important in the clinical handling of the patient. the description and the guidelines for treatment of the numerous clinical conditions potentially arising ina ssociation with the reactivation of the immune system in HIV-infected patients are given in the textbooks of

					infectious diseases. Hwever, as the clinical conditions associated with the reactivation of the immune system may constitute a threat to the patient, a reminder of the phenomenon is deemed of value and has been included in the SPC and PL of all antiretroviral medicinal products.
IB/0010	IB_42_a_01_Change in shelf-life of finished product - as packaged for sale	02/12/2004	n/a	SmPC	
S/0006	Annual re-assessment.	29/07/2004	15/10/2004	Annex II	
IA/0007	IA_05_Change in the name and/or address of a manufacturer of the finished product	21/09/2004	n/a		
II/0005	Update of Summary of Product Characteristics and Package Leaflet	22/04/2004	08/06/2004	SmPC and PL	
II/0002	Change(s) to the manufacturing process for the finished product Change(s) to the test method(s) and/or specifications for the active substance	24/03/2004	31/03/2004		
IA/0004	IA_43_a_01_ Add./replacement/del. of measuring or administration device - addition or replacement	02/02/2004	n/a	PL	
IA/0003	IA_38_a_Change in test procedure of finished product - minor change to approved test procedure	27/01/2004	n/a		
I/0001	12_Minor change of manufacturing process of the active substance	21/07/2003	30/07/2003		