Emselex

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/0075/G	This was an application for a group of variations. B.II.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	31/10/2023	n/a		

[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).

IAIN/0074	B.II.b.2.c.1 - Change to importer, batch release arrangements and quality control testing of the FP - Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing	26/10/2023	09/10/2024	Annex II and PL	
IAIN/0073/G	This was an application for a group of variations. A.1 - Administrative change - Change in the name and/or address of the MAH A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release	26/10/2023	09/10/2024	SmPC, Labelling and PL	
PSUSA/933/202110	Periodic Safety Update EU Single assessment - darifenacin	10/06/2022	n/a		PRAC Recommendation - maintenance
IB/0072/G	This was an application for a group of variations. 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.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	24/05/2022	n/a		
IAIN/0070/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of	04/02/2022	24/02/2023	Annex II and PL	

	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 B.II.b.2.c.1 - Change to importer, batch release arrangements and quality control testing of the FP - Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites				
T/0069	Transfer of Marketing Authorisation	04/02/2021	18/02/2021	SmPC, Labelling and PL	
IB/0068	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	10/11/2020	14/01/2021	SmPC and PL	
IAIN/0067	B.II.b.2.c.1 - Change to importer, batch release arrangements and quality control testing of the FP - Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing	27/01/2020	14/01/2021	Annex II and PL	
PSUSA/933/201810	Periodic Safety Update EU Single assessment - darifenacin	14/06/2019	n/a		PRAC Recommendation - maintenance
T/0065	Transfer of Marketing Authorisation	19/01/2018	15/02/2018	SmPC,	

				Labelling and PL	
IB/0064	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	19/12/2017	15/02/2018	SmPC, Annex II, Labelling and PL	
IB/0063/G	This was an application for a group of variations. B.II.b.1.e - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non-sterile medicinal products B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.4.a - Change in the batch size (including batch size ranges) of the finished product - Up to 10-fold compared to the originally approved batch size	09/11/2016	n/a		
II/0060	B.II.d.1.e - Change in the specification parameters and/or limits of the finished product - Change outside the approved specifications limits range	04/08/2016	n/a		
IAIN/0062	A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release	11/07/2016	23/06/2017	Annex II and PL	

PSUSA/933/201510	Periodic Safety Update EU Single assessment - darifenacin	09/06/2016	n/a		PRAC Recommendation - maintenance
IAIN/0061/G	This was an application for a group of variations. B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site	02/05/2016	n/a		
II/0058	B.I.a.1.g - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Introduction of a new manufacturer of the AS that is not supported by an ASMF and requires significant update to the relevant AS section in the dossier	24/09/2015	n/a		
N/0057	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	01/06/2015	23/06/2017	PL	
IAIN/0056	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	27/05/2015	n/a		
N/0055	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	22/10/2014	12/01/2015	PL	
IAIN/0054	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	13/10/2014	12/01/2015	SmPC and PL	

IAIN/0053	A.1 - Administrative change - Change in the name and/or address of the MAH	28/02/2014	12/01/2015	SmPC, Labelling and PL	
N/0052	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	13/12/2013	12/01/2015	PL	
IAIN/0051/G	This was an application for a group of variations. B.II.b.2.c.1 - Change to importer, batch release arrangements and quality control testing of the FP - Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing A.7 - Administrative change - Deletion of manufacturing sites 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	25/11/2013	12/01/2015	Annex II and PL	
T/0050	Transfer of Marketing Authorisation from Norvatis Europharm Ltd. to Merus Labs. Transfer of Marketing Authorisation	22/03/2013	22/04/2013	SmPC, Labelling and PL	
IB/0049/G	This was an application for a group of variations. B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.1.z - Change in the specification parameters	23/07/2012	n/a		

	and/or limits of the finished product - Other variation				
N/0048	Change in the Hungarian local representative's contact details in the package leaflet. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	10/01/2012	22/04/2013	PL	
II/0047	Update of Summary of Product Characteristics (SmPC) and Package Leaflet (PL). Changes to include adverse drug reaction "nasal dryness" in SmPC Section 4.8 and to include a warning on the risk of oedema of the tongue or laropharynx, or difficulty breathing in SmPC Section 4.4. The PL has been amended accordingly. Additionally, editorial and QRD template related changes are implemented in the SmPC and the PL, and contact details of the local representatives in Poland, Romania and Cyprus are 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	17/11/2011	14/12/2011	SmPC and PL	The MAH submitted a review of the data from the clinical trials and post-marketing reports for darifenacin in relation to nasal dryness and angioedema. Nasal dryness have been reported more frequently in association with use of darifenacin as compared to one antimuscarinic active control or placebo in clinical trials, and following post-marketing reports, therefore nasal dryness was included in the PI as an adverse reaction. The accumulated reports of angioedema were also analysed. Based on these findings, a warning has been was added to section 4.4 of the SmPC to stop the treatment with darifenacin in case oedema of the tongue or laropharynx, or difficulty breathing develops. This was endorsed by the CHMP.
II/0046	Update of section 4.8 of the SmPC to include the post-marketing adverse drug reactions "mood alteration/depressed mood" and "hallucinations". This variation application is submitted further to the request of the CHMP following assessment of PSUR Nr. 8, covering the period 1st November 2008 - 31st October 2009. The package leaflet has been amended accordingly.	18/11/2010	20/12/2010	SmPC and PL	A cumulative database search performed by he MAH identified 45 post-marketing reports pertaining to the topic of depressed mood or mood alteration. 20 of them were serious and 25 non-serious. Fourteen reports had insufficient information for a medical evaluation, 26 described other ADRs. 16 reports of hallucinations were retrieved using the MedDRA High level term 'Perception disturbances'. 6 of

	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				them described a positive de-challenge suggesting a possible causal relationship with Emselex treatment. Based on this information "mood alteration/depressed mood" and "hallucinations" are added to section 4.8 of the SmPC.
IA/0042	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site IA_07_b_01_Replacement/add. of manufacturing site: Primary packaging site - Solid forms	07/01/2010	n/a		
N/0041	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	09/12/2009	n/a	PL	
R/0039	Renewal of the marketing authorisation.	25/06/2009	24/09/2009	SmPC, Annex II, Labelling and PL	Based on the review of the available information the CHMP is of the opinion that the quality, the safety and the efficacy of this medicinal product continues to be adequately and sufficiently demonstrated and therefore considers that the benefit/risk profile of Emselex continues to be favorable. The CHMP was of the opinion that the renewal could be granted with unlimited validity. However the MAH will continue to submit yearly PSURs, unless otherwise specified by the CHMP. The MAH also provided a new reworded text for the section 4.6 Fertility, Pregancy and lactation and 5.3 Pre-clinical safety data of the SPC according to the new guideline on reproductive toxicity data and labeling. Fertility data have been included; the information on the use in pregnancy has

					been updated.
II/0040	Update of the section 4.4 of the Summary Product Characteristics to add a cautionary statement on use in patients with pre-existing cardiac diseases. The Package Leaflet has been updated accordingly. Update of Summary of Product Characteristics and Package Leaflet	25/06/2009	31/07/2009	SmPC and PL	Following the assessment of a phase IV study in elderly patients ? 65 years old, the CHMP requested to add a cautionary statement on use in patient with pre-existing cardiac diseases in the SPC. The results of the study indicated there was a higher incidence of cardiac adverse events, mainly due to supraventricular (SV) arrhythmias among DRF-treated patients compared to placebo. The section 4.4 has been updated as follow: "Caution should be used when prescribing antimuscarinics to patients with pre-existing cardiac diseases"
IA/0038	IA_09_Deletion of manufacturing site	05/03/2009	n/a		
IA/0037	IA_09_Deletion of manufacturing site	16/09/2008	n/a		
IA/0036	IA_09_Deletion of manufacturing site	15/09/2008	n/a		
II/0034	Update of Summary of Product Characteristics and Package Leaflet	24/07/2008	25/08/2008	SmPC and PL	
IA/0035	IA_11_a_Change in batch size of active substance or intermediate - up to 10-fold	19/06/2008	n/a		
II/0032	Update of Section 4.8 'Undesirable effects' of the SPC with the addition of 'hypersensitivity reactions' including 'angioedema' following review of data from clinical trials and postmarketing experience. Section 4 of the PL has been amended accordingly. In addition, 'dry mouth' and 'constipation', already included in section 4.8 of the SPC, were reflected in	19/03/2008	23/04/2008	SmPC and PL	

	the corresponding Adverse Drug Reaction (ADR). Update of Summary of Product Characteristics and Package Leaflet				
IA/0033	IA_11_b_Change in batch size of active substance or intermediate - downscaling	06/03/2008	n/a		
N/0028	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	17/12/2007	n/a	PL	
IA/0030	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	30/11/2007	n/a		
IA/0027	IA_07_b_01_Replacement/add. of manufacturing site: Primary packaging site - Solid forms	09/10/2007	n/a		
N/0024	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	09/08/2007	n/a	PL	
IA/0026	IA_05_Change in the name and/or address of a manufacturer of the finished product	26/06/2007	n/a		
IA/0025	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	26/06/2007	n/a		
II/0023	Update of section 4.8 of the Summary of Products Characteristics (SPC) and section 4 of Patient Leaflet (PL) further to the assessment of the 3rd PSUR. The Product Information has been updated in accordance to the QRD template version 7.2. In addition, the contact details of the Hungarian local representative	22/02/2007	23/03/2007	SmPC, Annex II, Labelling and PL	Further to the assessment of the 3rd PSUR the section 4.8 of the SPC has been updated to include urinary retention and blurred vision as uncommon adverse drug reactions. Finally, section 4 of the PL has also been updated accordingly.

	have been changed and the contact details of Bulgarian and Romanian local representatives included in the PL. Update of Summary of Product Characteristics, Labelling and Package Leaflet				
II/0022	This variation refers to an update of sections 4.5, 4.7, 4.8 and 5.2 of the Summary of Product Characteristics (SPC) following a Review of available safety information by the MAH (Marketing Authorisation Holder). The Package Leaflet has been updated accordingly. In addition to this, the MAH changed the local representative in Portugal. Update of Summary of Product Characteristics and Package Leaflet	18/10/2006	29/11/2006	SmPC and PL	Following a review of all available safety information, the MAH submitted a Type II Variation in order to reflect the changes introduced in the company's core data sheet. The following sections have been updated: Section 4.5. Interaction with other medicinal products and other forms of interaction For clarity and consistency, the darifenacin exposure in the presence of paroxetine has been updated to better reflect the results of a randomised placebo controlled, parallel group study to investigate the effects of paroxetine on the pharmacokinetics, pharmacodynamics, safety and tolerability of darifenacin at steady state (protocol A1371008), submitted as part of the original application. In addition, ritonavir is also listed as one potent CYP3A4 inhibitor. Section 4.7. Effects on ability to drive and use machines Information have been included to reflect that patients experiencing effects such as dizziness, blurred vision, insomnia and somnolence should not drive or use machines. Section 4.8. Undesirable effects Included information in relation to the frequency of the most commonly reported adverse drug reactions (dry mouth and constipation) based on the data from a flexible dose titration study.

					Section 5.2. Pharmacokinetics The MAH also updated section 5.2 of the SPC (Pharmacokinetics Properties) to include information on the elimination half-life of darifenacin following chronic dosing and on protein binding of darifenacin in patients with moderate hepatic impairment. The Package Leaflet has been updated accordingly.
II/0021	Quality changes	28/06/2006	03/07/2006		
N/0020	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	18/05/2006	n/a	PL	
II/0010	Update and/or changes of pharmaceutical documentation Quality changes	13/10/2005	17/11/2005	SmPC, Labelling and PL	
II/0009	Quality changes	13/10/2005	20/10/2005		
II/0015	Quality changes	15/09/2005	23/09/2005		
IA/0019	IA_29_b_Change in qual./quant. composition of immediate packaging - all other pharm. forms	23/09/2005	23/09/2005	SmPC	
IB/0014	IB_37_b_Change in the specification of the finished product - add. of new test parameter	15/08/2005	n/a		
IB/0013	IB_37_b_Change in the specification of the finished product - add. of new test parameter	15/08/2005	n/a		

IB/0012	IB_38_c_Change in test procedure of finished product - other changes	15/08/2005	n/a		
IB/0011	IB_38_c_Change in test procedure of finished product - other changes	15/08/2005	n/a		
IB/0008	IB_07_c_Replacement/add. of manufacturing site: All other manufacturing operations ex. batch release	15/08/2005	n/a		
IA/0017	IA_07_b_01_Replacement/add. of manufacturing site: Primary packaging site - Solid forms	22/07/2005	n/a		
IA/0016	IA_07_b_01_Replacement/add. of manufacturing site: Primary packaging site - Solid forms	22/07/2005	n/a		
IA/0007	IA_08_b_01_Change in BR/QC testing - repl./add. manuf. responsible for BR - not incl. BC/testing	22/07/2005	n/a	Annex II and PL	
IA/0004	IA_07_b_01_Replacement/add. of manufacturing site: Primary packaging site - Solid forms	22/07/2005	n/a		
IB/0003	IB_17_a_Change in re-test period of the active substance	05/07/2005	n/a		
IA/0002	IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size	27/05/2005	27/05/2005	SmPC, Labelling and PL	
N/0001	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	20/12/2004	n/a	PL	