EXJADE

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/0091/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.2.c.1 - Change to importer, batch release	13/12/2024		Annex II and PL	

[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).

	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 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 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				
IA/0089	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	01/07/2024	n/a		
IA/0088	A.7 - Administrative change - Deletion of manufacturing sites	13/06/2024	n/a		
IG/1724/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging	26/03/2024	n/a		

	site				
IA/0086/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.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.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	27/02/2024	n/a		
II/0085	Submission of an updated RMP version 21.2 in order to include the physician survey CICL670A2429 as a PASS category 3, based on the submission of a draft version of the protocol for the physician survey CICL670A2429. The Annex IID is updated to remove one sentence related to 'surveillance programme' and to introduce a minor correction to the guide for healthcare professionals.	28/09/2023	01/10/2024	Annex II	

	C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required				
PSUSA/939/202210	Periodic Safety Update EU Single assessment - deferasirox	08/06/2023	n/a		PRAC Recommendation - maintenance
II/0082/G	This was an application for a group of variations. C.I.13: Submission of the final report from the Calypso study (CICL670F2202) listed as a category 3 study in the RMP. This is a randomized, open-label, multicenter, two arm, Phase II study to evaluate treatment compliance, efficacy and safety of deferasirox (granules) in pediatric patients with iron overload. The RMP version 20.0 has also been submitted. C.I.11.b: Submission of an updated RMP version 20.0 which the following changes: to remove the risk of 'medication error' from the Exjade RMP and to remove the information related to the discontinuation of Exjade Dispersible Tablets in the EU. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing	21/07/2022	25/08/2022	SmPC, Annex II and PL	Submission of study F2202, a randomized, open-label, multicenter, two-arm, Phase II study whose aim was to evaluate the safety of deferasirox (DFX) granules versus deferasirox dispersible tablets (DTs) in paediatric patients with iron overload. Updated PK information of Study F2202 indicated no significant difference in PKs characteristics in the paediatric target patients. the safety profile of deferasirox administered as DT or as granules was similar, and consistent with the known safety profile of deferasirox. Section 4.2 of the SmPC and section 3 of the PL were updated to highlight that a 30% dose reduction is needed in case of a switch between DT formulation and FCT/granules formulations. The EURD list is updated to include all generic marketing authorisation holders in the next PSURs. Please refer to Scientific Discussion 'Product Name-H-C-Product Number-II-Var.No' For more information, please refer to the Summary of Product Characteristics.

	authorisation, including the RMP - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required				
IG/1521	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	23/06/2022	n/a		
IB/0081	C.I.7.a - Deletion of - a pharmaceutical form	21/12/2021	24/01/2022	SmPC, Annex II, Labelling and PL	
IA/0080	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	25/08/2021	n/a		
IB/0079/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.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	09/08/2021	15/09/2021	Annex II and PL	

	manufacturing sites B.II.b.4.b - Change in the batch size (including batch size ranges) of the finished product - Downscaling down to 10-fold 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.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation B.II.c.1.z - Change in the specification parameters and/or limits of an excipient - Other variation				
II/0075	The PI has been updated to remove discrepancies between SmPC and PL in sections `Pregnancy and breast-feeding' and section `Other medicines and EXJADE'. Furthermore, the Exjade SmPC and PL have been updated according to the Guidelines on excipients in the labelling and package leaflet of medicinal products for human use, Rev. 2. The MAH took also the opportunity to align the PI with the latest QRD template v. 10.1 and update the details of local representatives in EE, LV and NL.	11/03/2021	15/09/2021	SmPC, Annex II, Labelling and PL	SmPC new text The following information relevant for the prescribers has been included in the SmPC: This medicinal product contains less than 1 mmol sodium (23 mg) per dispersible tablet, that is to say essentially 'sodium free'. For more information, please refer to the Summary of Product Characteristics. The due date of the Annex II D commitment to assess the long term exposure and safety of deferasirox dispersible and film coated tablets, the MAH should conduct an observational cohort study in paediatric non transfusion

	The Annex IID has been updated to reflect the new milestone for study CICL670E2422. In addition, the EU RMP version 18.0 for Exjade has been revised to introduce following changes: · Removal of the important identified risk, "Severe cutaneous adverse reactions (including Stevens-Johnson syndrome, Toxic epidermal necrolysis and Drug reaction with eosinophilia and systemic symptoms)" · Change to the milestone for Study CICL670E2422 (Category 1) and change to RMP commitment deliverable and milestone for Study CICL670F2202 (Category 3) · Removal of the study CICL670F2429 (Category 1) due to fulfilment of the corresponding Post-Authorisation Measure · Removal of the expedited reporting requirement for the serious Adverse Drug Reactions (ADRs), 'Increase in hepatic enzymes >10 x upper limit of normal (ULN)', 'Serious rise in creatinine', 'results of renal biopsies', 'cataracts', 'hearing loss', gallstones' as agreed during PRAC PSUR Assessment (Procedure no.: EMEA/H/C/PSUSA/00000939/201910). Amendments to the marketing authorisation The variation introduces changes to the Annex IID, SmPC, Labelling, Package leaflet and the RMP. C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of				dependent thalassaemia patients over 10 years old for whom deferoxamine is contraindicated or inadequate conducted according to a CHMP agreed protocol, has been revised to July 2025.

	change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required				
IB/0078/G	This was an application for a group of variations. A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient B.I.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 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	18/12/2020	n/a		
II/0068	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	26/11/2020	n/a		
IA/0077	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	20/11/2020	n/a		

IA/0076	B.II.e.6.b - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that does not affect the product information	19/11/2020	n/a		
II/0073	Submission of the final study report from the post-authorisation pharmacovigilance measure in the Annex II and in the RMP, a single-arm interventional Phase IV, evaluating the safety of pediatric patients with transfusional hemosiderosis treated with deferasirox crushed film-coated tablets. This submission also serves to comply with Article 46 of the Regulation (EC) No 1901/2006 on medicinal products for pediatric use. C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	03/09/2020	15/09/2021	Annex II	In this variation the obligation to conduct the safety study (PASS) to assess the safety of deferasirox film coated tablets in the paediatric population (especially when the tablets are crushed) has been fulfilled and the Annex II updated accordingly.
IB/0074/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites 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 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	18/08/2020	n/a		

	batch control/testing takes place B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS 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.4.c - Change to in-process tests or limits applied during the manufacture of the AS - Deletion of a non-significant in-process test 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.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure 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 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 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				
PSUSA/939/201910	Periodic Safety Update EU Single assessment - deferasirox	28/05/2020	31/07/2020	SmPC and	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)’ for

				Annex II	PSUSA/939/201910.
IAIN/0072/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites 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.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.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	20/05/2020	31/07/2020	Annex II and PL	
IB/0071/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) 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) A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites	19/03/2020	n/a		

	(excluding manufacturer for batch release) A.7 - Administrative change - Deletion of manufacturing sites				
IAIN/0070/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 B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place	27/01/2020	n/a		
II/0066	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	25/07/2019	31/07/2020	SmPC	
PSUSA/939/201810	Periodic Safety Update EU Single assessment - deferasirox	29/05/2019	19/07/2019	SmPC, Annex II and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/939/201810.
II/0064	C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of	14/06/2019	n/a		

	change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required				
IG/1099	A.7 - Administrative change - Deletion of manufacturing sites	24/05/2019	n/a		
N/0063	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	05/10/2018	19/07/2019	Labelling	
II/0061	B.I.z - Quality change - Active substance - Other variation	20/09/2018	n/a		
PSUSA/939/201710	Periodic Safety Update EU Single assessment - deferasirox	31/05/2018	23/07/2018	SmPC and PL	Please refer to EXJADE PSUSA-00000939-201710 EPAR: Scientific conclusions and grounds recommending the variation to the terms of the marketing authorisation
IG/0950	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)	18/06/2018	n/a		
IB/0060	B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	03/05/2018	n/a		
T/0059	Transfer of Marketing Authorisation	26/03/2018	19/04/2018	SmPC, Labelling and PL	
IA/0058/G	This was an application for a group of variations. A.4 - Administrative change - Change in the name	07/02/2018	n/a		

	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.7 - Administrative change - Deletion of manufacturing sites				
X/0054	Annex I_2.(a) Change of bioavailability Annex I_2.(d) Change or addition of a new pharmaceutical form	14/09/2017	10/11/2017	SmPC, Annex II, Labelling and PL	Please refer to Scientific Discussion Exjade-H-670-X-54-AR.
PSUSA/939/201610	Periodic Safety Update EU Single assessment - deferasirox	22/06/2017	14/08/2017	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/939/201610.
II/0052	Update of sections 4.4 and 5.1 of the SmPC with corresponding warnings and final results of study ICL670F2201, a randomized, open-label, multi-center, two-arm phase II study to evaluate the safety of deferasirox film-coated tablets (FCT) formulation and deferasirox dispersible tablet (DT) formulation in patients with transfusion dependent thalassemia or myelodysplastic syndrome (MDS) at very low, low or intermediate risk requiring chelation therapy due to iron overload. The MAH also took the opportunity to update Annex II with the fulfilment of the obligation. The Risk Management Plan (RMP, v.14) is updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	26/01/2017	14/08/2017	SmPC and Annex II	The MAH submitted the final clinical study report for study CICL670F2201: a post-authorisation pharmacovigilance phase II study to confirm the clinical safety results of the new film-coated tablets (FCT) formulation, requested as part of the line extension procedure EMEA/H/C/000670/X/43. Overall although the data remains limited, no apparent new safety signal has been identified from the study results. A summary of the main study results have been included in section 5.1 'Pharmacodynamic properties' of the SmPC as follows: In a study to assess the safety of deferasirox film-coated and dispersible tablets, 173 adult and paediatric patients with transfusion dependent thalassaemia or myelodysplastic syndrome were treated for 24 weeks. A comparable safety profile for film-coated and dispersible tablets was observed. In addition, in section 4.4 'Special warnings and precautions' of the SmPC, in the existing warning on renal

					function, it has been clarified that the recommendations on renal function monitoring also apply in case of switch of formulation (from dispersible to film-coated tablets). Finally the summary of the main study results from study A2411 included in the Paediatric Investigation Plan have been moved from section 4.8 'Undesirable effects' to section 5.1 'Pharmacodynamic properties' of the SmPC at the CHMP's request.
IB/0055	B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation	04/01/2017	n/a		
II/0050	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	10/11/2016	n/a		
II/0048	Update of section 4.4 and 4.8 of the SmPC in order to add information on paediatric population from the final results of study A2411 from the Paediatric Investigation Plan EMEA-001103-PIP01-10-M02. This submission serves to comply with Article 46 of the Regulation (EC) No 1901/2206 on medicinal products for paediatric use. Consequently, the RMP v.12.2 is presented. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	06/10/2016	14/08/2017	SmPC	In two clinical studies, growth and sexual development of paediatric patients treated with deferasirox for up to 5 years were not affected. In a 5-year observational study in which 267 children aged 2 to <6 years (at enrollment) with transfusional haemosiderosis received deferasirox, there were no clinically meaningful differences in the safety and tolerability profile of Exjade in paediatric patients aged 2 to <6 years compared to the overall adult and older paediatric population, including increases in serum creatinine of >33% and above the upper limit of normal on ≥2 consecutive occasions (3.1%), and elevation of alanine aminotransferase (ALT) greater than 5 times the upper limit of normal (4.3%). Single events of increase in ALT and aspartate aminotransferase were reported in 20.0% and 8.3%, respectively, of the 145 patients who completed

					the study.
IB/0053	B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation	16/09/2016	n/a		
II/0051	C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required	15/09/2016	n/a		
PSUSA/939/201510	Periodic Safety Update EU Single assessment - deferasirox	26/05/2016	15/07/2016	SmPC and PL	Please refer to Exjade-PSUSA/939/201510 EPAR: Scientific conclusions and grounds recommending the variation to the terms of the marketing authorisation.
R/0047	Renewal of the marketing authorisation.	25/02/2016	18/04/2016	SmPC, Annex II, Labelling and PL	Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of Exjade in the approved indications remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.
X/0043	Annex I_2.(a) Change of bioavailability Annex I_2.(c) Change or addition of a new strength/potency Annex I_2.(d) Change or addition of a new pharmaceutical form	28/01/2016	22/03/2016	SmPC, Annex II, Labelling and PL	Please refer to Scientific Discussion Exjade-H-670-X-43-AR.
II/0045	Update of sections 4.2 and 4.4 of the SmPC in order to improve readability, based on results from studies CICL670A2425, CICL670A2426 and CICL670AFR01T and patient survey. The submission serves also to comply with article 46 of the regulation (EC) N°	28/01/2016	22/03/2016	SmPC, Annex II and PL	As a result of this variation, section 4.2 and 4.4 of the SmPC of Exjade is being updated to simplify the language and improve prescribers' awareness for posology criteria for both TDT and NTDT patients, readability for parameters leading to dose reduction and treatment interruption, to

	1901/2206 (as amended) on medicinal products for paediatric use following the paediatric data from studies CICL670A2426 and CICL670AFR01T. The Package Leaflet and Annex II are updated accordingly. The updated RMP version 11.1 has been agreed. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				correct some inconsistencies, to improve clarity for biological/clinical monitoring and to delete the recommendations that the results of the biological tests should be noted in the patient's booklet. Changes are made to the Opinion Annex II conditions to extend the distribution of educational materials adding periodic distributions of educational materials after launch, notably after substantial product information modifications related to safety. Combination of key elements of TDT and NTDT indications into one educational prescribers' brochure has also been proposed. Diary part and patient reminder card have been deleted from the patient educational pack.
PSUSA/939/201410	Periodic Safety Update EU Single assessment - deferasirox	21/05/2015	17/07/2015		Please refer to Exjade-PSUSA-00000939-201410 EPAR: Scientific conclusions and grounds recommending the variation to the terms of the marketing authorisation
IA/0046	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)	07/07/2015	n/a		
IB/0044	B.II.e.5.a.2 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change outside the range of the currently approved pack sizes	28/04/2015	17/07/2015	SmPC, Labelling and PL	
IB/0041/G	This was an application for a group of variations. B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement	03/02/2015	n/a		

	or addition) for the AS or a starting material/intermediate 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.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				
IB/0040/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.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	18/12/2014	n/a		
IAIN/0039	A.1 - Administrative change - Change in the name and/or address of the MAH	06/11/2014	17/07/2015	SmPC, Labelling and PL	

PSUV/0037	Periodic Safety Update	26/06/2014	04/09/2014		Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUV/0037.
IAIN/0038	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	28/03/2014	n/a		
II/0036/G	This was an application for a group of variations. Update of section 4.4 and 4.8 of the SmPC with regard to Stevens-Johnson Syndrome following cases reported in the post-marketing setting. The package leaflet is updated accordingly. Update of section 4.4 of the SmPC to add a summary table of safety monitoring recommendations and of section 4.8 of the SmPC with regard to pancreatitis further to the request of the PRAC in the assessment of PSUR 10. The conditions for safe and effective use in Annex II are also updated after completion of enrolment of relevant studies. The MAH also took the opportunity to update the product information in line with QRD template version 9.0 and to update the list of local representatives in the package leaflet. C.I.3.z - 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 - Other variation C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-	19/09/2013	28/04/2014	SmPC, Annex II and PL	Cases of Stevens-Johnson syndrome (SJS) have been reported post marketing. If SJS is suspected, EXJADE should be discontinued immediately and should not be reintroduced. Serious acute pancreatitis may potentially occur as a complication of gallstones (and related biliary disorders) which are known effects of Exjade. Existing safety monitoring recommendations with Exjade has been summarised in tabular format in section 4.4 of the SmPC for ease of reference.

	clinical, clinical or pharmacovigilance data				
II/0025	Update of section 4.8 of the SmPC to include a description of the magnitude of the effect on estimated renal clearance based on a retrospective meta-analysis of 2,102 beta-thalassemia major patients exposed to deferasirox in 6 completed clinical trials. The Marketing Authorisation Holder also took the opportunity to update the product information with version 8.3 of the QRD template. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	25/04/2013	28/04/2014	SmPC and Annex II	TThe MAH applied to remove the restriction of indication "when deferoxamine therapy is contraindicated or inadequate", thus for the use of deferasirox in first-line in infrequently-transfused patients beta-thalassemia major patients aged 6 years and older. This application was supported by an analysis of 2,102 beta-thalassemia major patients exposed to deferasirox in 6 completed clinical trials. Further to the assessment of the CHMP that this extension of the indication was not considered approvable, the MAH decided not to pursue with the proposed change to the indication. However, the CHMP agreed to the proposal from the MAH to include a description of the magnitude of the effect on estimated renal clearance based on the retrospective meta-analysis in section 4.8 of the SmPC. Please refer to Scientific Discussion Exjade-H-670-II-25-AR.
IG/0248	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	17/12/2012	n/a		
II/0026	New indication of Exjade for the treatment of chronic iron overload requiring chelation therapy when deferoxamine therapy is contraindicated or inadequate in patients with non-transfusion-dependent thalassaemia syndromes aged 10 years and older. Consequently, sections 4.1, 4.2, 4.4, 4.8 and 5. of the SmPC and the package leaflet have been updated. Annex II has also been updated to	15/11/2012	20/12/2012	SmPC, Annex II, Labelling and PL	Please refer to Scientific Discussion Exjade-H-670-II-26-AR.

	include an obligation to conduct a post-authorisation measure. The Marketing Authorisation Holder also took the opportunity to update the product information with the latest QRD template (version 8.1). C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
II/0031	Update of section 4.4 and 4.8 of the SmPC with regard to aggravated anaemia, further to a request of the CHMP in the assessment of the 9th PSUR. The Package Leaflet was updated accordingly. Section 4.6 of the SPC was updated to reflect information included in section 4.5 on interaction with hormonal contraceptives. In addition, the MAH took the opportunity to make editorial changes to the SmPC and update the contact details of Malta in the list of local representatives in the Package Leaflet. C.I.3.z - 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 - Other variation	20/09/2012	24/10/2012	SmPC and PL	A review of the cases of aggravated anaemia/haemoglobin decreased was conducted by the marketing authorisation holder, at the request of the CHMP. Although, in most cases, confounding factors such as underlying diseases were identified, a close temporal relationship was noted in many cases. In some of them, Exjade administration was associated with an increased frequency of blood transfusions and/or positive dechallenge was noted. Thus the responsibility of Exjade as contributing or aggravating factor cannot be ruled out. Therefore, the CHMP considered that update of the product information was required. Section "Fertility, pregnancy and lactation" of the Summary of Product Characteristics was amended to reflect that Exjade may decrease the efficacy of hormonal contraceptives.
IB/0032/G	This was an application for a group of variations. B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation B.I.b.1.c - Change in the specification parameters	21/09/2012	n/a		

	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 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 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 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 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 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 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 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				
IB/0034/G	This was an application for a group of variations. B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	11/09/2012	n/a		
IG/0209/G	This was an application for a group of variations. C.I.9.b - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the contact details of the QPPV C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s)	17/08/2012	n/a		

	to the DDPS that does not impact on the operation of the pharmacovigilance system				
IB/0029/G	This was an application for a group of variations. 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.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition) 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	07/08/2012	n/a		
IA/0030	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	27/07/2012	n/a		
IG/0148/G	This was an application for a group of variations.	22/02/2012	n/a		

	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 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				
II/0022	Update of sections 4.2, 4.4 and 5.2 of the SmPC with recommendation regarding the use of Exjade in patients with hepatic impairment further to results of a pharmacokinetic study in patients with varying degrees of hepatic impairment. The MAH also took the opportunity to include the date of the last renewal in 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	17/11/2011	19/12/2011	SmPC	In a clinical study using single doses of 20 mg/kg deferasirox, the average exposure was increased by 16% in subjects with mild hepatic impairment (Child-Pugh Class A) and by 76% in subjects with moderate hepatic impairment (Child-Pugh Class B) compared to subjects with normal hepatic function. The average Cmax of deferasirox in subjects with mild or moderate hepatic impairment was increased by 22%. Exposure was increased 2.8-fold in one subject with severe hepatic impairment (Child-Pugh Class C). Therefore, EXJADE is not recommended in patients with severe hepatic impairment (Child-Pugh Class C). In patients with moderate hepatic impairment (Child-Pugh Class B), the dose should be considerably reduced followed by progressive increase up to a limit of 50% (see sections 4.4 and 5.2), and EXJADE must be used with caution in such patients. Hepatic function in all patients should be monitored before treatment, every 2 weeks during the first month and then every month. The Product Information has been updated accordingly.

R/0021	Renewal of the marketing authorisation.	19/05/2011	27/07/2011	SmPC, Annex II and PL	Based upon the data that have become available since the granting of the initial Marketing Authorisation, the CHMP considers that the benefit-risk balance of Exjade remains positive, but considers that its safety profile is to be closely monitored for the following reasons: Renal toxicity is a particular safety issue which could impact on the benefit-risk balance of Exjade. This is an important identified risk in the RMP (serum creatinine increased, ARF, renal tubulopathy), which should continue to be closely monitored. The CHMP decided that the MAH should continue to submit yearly PSURs. Therefore, based upon the safety profile of Exjade, which requires the submission of yearly PSURs, the CHMP concluded that the MAH should submit one additional renewal application in 5 years time.
IG/0088/G	This was an application for a group of variations. 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 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	11/07/2011	n/a		
IG/0032/G	This was an application for a group of variations.	21/12/2010	n/a		

	To update the Detailed Description of the Pharmacovigilance System (DDPS) to version 9.0, to include: - a change in the deputy of the Qualified Person for Pharmacovigilance (QPPV); - a change in the major contractual arrangements. - administrative changes not impacting the operation of the pharmacovigilance system. Annex II.B has also been updated with the latest wording as per October 2010 CHMP procedural announcement. 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.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 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				
II/0020	Update to sections 4.4 and 4.5 of the Summary of Product Characteristics to include results of study ICL670A2131 investigating the effect of deferasirox on pharmacokinetics of theophylline (CYP1A2 substrate) in healthy volunteers, conducted at the	18/11/2010	20/12/2010	SmPC, Annex II, Labelling and PL	Further to the request of the CHMP, the MAH has conducted Study ICL670A2131, a Phase I open-label, one-sequence, two-period study conducted to assess the effect of Exjade (deferasirox) on pharmacokinetics of theophylline in healthy volunteers.

	request of the CHMP further to the assessment of FUM 010. The Package Leaflet has been updated accordingly. The MAH also took the opportunity to update the product information in line with version 7.3.1 of the QRD template, to delete the version number of the DDPS from Annex II and to update the local representative's contact details for Cyprus in the package leaflet. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				In this healthy volunteer study, the concomitant administration of Exjade as a CYP1A2 inhibitor (repeated dose of 30 mg/kg/day) and the CYP1A2 substrate theophylline (single dose of 120 mg) resulted in an increase of theophylline AUC by 84% (90% CI: 73% to 95%). The single dose Cmax was not affected, but an increase of theophylline Cmax is expected to occur with chronic dosing. Therefore, the concomitant use of Exjade with theophylline is not recommended. If Exjade and theophylline are used concomitantly, monitoring of theophylline concentration and theophylline dose reduction should be considered. An interaction between Exjade and other CYP1A2 substrates cannot be excluded. For substances that are predominantly metabolised by CYP1A2 and that have a narrow therapeutic index (e.g. clozapine, tizanidine), the same recommendations apply as for theophylline. Sections 4.4 and 4.5 of the Summary of Product Characteristics and the Package Leaflet have been updated accordingly in this respect.
II/0019	Update of the Detailed Description of the Pharmacovigilance system (DDPS) to version 8.0, including a change of the Qualified Person for Pharmacovigilance (QPPV). Consequently, Annex II has been updated with the new version number of the agreed DDPS, in accordance with QRD template version 7.3. Changes to QPPV Update of DDPS (Pharmacovigilance)	18/02/2010	15/03/2010	Annex II	With this variation the MAH submitted a new version of the DDPS (core version 8.0) in accordance with the current Pharmacovigilance guideline. After assessing the documentation the CHMP concluded that the submitted DDPS contained all required elements.

II/0016	Introduction of a Design Space and real time release for the finished product. Quality changes	17/12/2009	13/01/2010		
II/0018	Update of Summary of Product Characteristics and Package Leaflet	22/10/2009	23/11/2009	SmPC and PL	The CHMP agreed to update the SPC sections 4.2, 4.4, 4.8 and 5.2 following safety information resulting from PSURs 6 and 7 and from supportive safety analyses. The following sections of the SPC are amended in this application : - addition of precautionary statement about higher frequency of adverse drug reactions in elderly patients and about the occurrence of renal tubulopathy in young thalassemia patients with low serum ferritin levels (section 4.4 and 4.2) -clarification of monitoring requirements for hepatic function (section 4.2) - addition of warning for patients with advanced malignancies and limited life expectancy (section 4.4) - addition of warning on rare reports of fatal gastrointestinal haemorrhages, especially in elderly patients who had advanced haematologic malignancies and/or low platelet counts, and caution in patients with low platelet counts (section 4.4) - addition of information on a longer observation period for the absence of effects on paediatric growth and development (section 4.4) - addition of erythema multiforme and alopecia to section 4.8 - addition of information on the degree of enterohepatic recycling, as determined in a recent study with

					cholestyramine (section 5.2) The Package Leaflet is also amended consequently. Furthermore, minor editorial changes were applied and the list of local representatives in the Package Leaflet has been updated for Estonia, Finland, Latvia and Slovenia.
II/0009	Update of Summary of Product Characteristics and Package Leaflet	22/10/2009	23/11/2009	SmPC and PL	Amendment of Section 4.2 of the SPC to extend the recommended dose range for maintenance therapy to a maximum of 40 mg/kg/day for patients not adequately controlled with doses of 30 mg/kg. However it is highlighted that the current efficacy and safety data are limited and if very poor control is achieved at doses up to 30 mg/kg, a further increase to 40mg/kg may not achieve satisfactory control, alternative treatment options may be considered. Doses above 40 mg/kg are not recommended because there is only limited experience with doses above this level. Amendment of section 4.4 of the SPC to introduce a warning that increased risk of renal adverse events with EXJADE doses above 30 mg/kg cannot be excluded. The Package Leaflet has been updated accordingly.
II/0017	Further to CHMP request related to the PSUR covering the period 01.11.07 to 30.04.08, the MAH submitted an update of Section 4.4 of the SPC. Update of Summary of Product Characteristics	25/06/2009	14/07/2009	SmPC	Update of Summary of Product Characteristics: The CHMP agreed to update of Section 4.4 of the SPC, regarding post-marketing cases of renal function deterioration leading to renal failure requiring temporary or permanent dialysis.

II/0014	The MAH has applied for changes related to the implementation of Quality by Design and Quality Risk Management principles in the manufacturing of drug substance. Quality changes	25/06/2009	06/07/2009		
II/0015	Update of Sections 4.4 and 4.8 of the SPC to implement safety changes and add a warning regarding cases of "pancytopenia" as requested by the CHMP further to the assessment of the 5th PSUR. In addition "leukocytoclastic vasculitis" and thrombocytopenia are added to the Section 4.8 of the SPC. The Package Leaflet is updated accordingly. Update of Summary of Product Characteristics and Package Leaflet	19/02/2009	25/03/2009	SmPC and PL	Based on the data provided by the MAH, the CHMP agreed on the following changes to the SPC and PI accordingly. Update of section 4.4 (Special warnings and precautions for use): There have been post-marketing reports (both spontaneous and from clinical trials) of pancytopenia or aggravation of pancytopenia in patients treated with EXJADE. Most of these patients had pre-existing haematological disorders that are frequently associated with bone marrow failure. However, the responsibility of Exjade as an aggravating or a contributing factor cannot be ruled out. Interruption of treatment should be considered in patients who develop unexplained pancytopenia. Update of section 4.8 (Undesirable effects): Addition of pancytopenia and thrombocytopenia as follows : Blood and Lymphatic system disorders: Not known : pancytopenia (see section 4.4), thrombocytopenia Addition of leukocytoclastic vasculitis as follows: Skin and subcutaneous tissue disorders

					Not known: leukocytoclastic vasculitis
II/0010	Update of Summary of Product Characteristics and Package Leaflet: Amendment of Sections 4.4 and 4.5 of the SPC following results from two clinical studies on drug-drug interaction to investigate the effect of rifamficin (potent UGT inducer) and repaglinide (Cyp2C8 probe substrate). The CHMP requested the MAH to update the Product Information following previous assessment of these two clinical studies as Follow Up Measures. The Package Leaflet has been updated accordingly. In addition, minor QRD corrections were made in Sections 4.4 and 4.5 of the SPC. Update of Summary of Product Characteristics and Package Leaflet	20/11/2008	17/12/2008	SmPC and PL	The CHMP introduced updated information on warning regarding potential interactions with potent UGT inducer and CYP2C8 substrates: Update of section 4.4 Caution should be exercised when deferasirox is combined with strong UDP-glucuronosyl transferase (UGT) inducers, or CYP2C8 substrates (see section 4.5). Update of section 4.5 The CHMP introduced updated information on drug interaction with rifampicin (potent UGT inducer): In a healthy volunteer study, the concomitant administration of deferasirox (single dose of 30 mg/kg) and the potent UGT inducer, rifampicin, (repeated dose of 600 mg/day) resulted in a decrease of deferasirox exposure by 44% (90% CI: 37% - 51%). Therefore, the concomitant use of deferasirox with potent UGT inducers (e.g. rifampicin, carbamazepine, phenobarbital, phenytoin, ritonavir) may result in a decrease in EXJADE efficacy (see section 4.4). The CHMP introduced updated information on drug interaction with repaglinide (CYP2C8 substrate) "In a healthy volunteer study, the concomitant administration of deferasirox as a moderate CYP2C8 inhibitor (30 mg/kg daily), with repaglinide, a CYP2C8 substrate, given as a single dose of 0,5 mg, increased

					repaglinide AUC and Cmax about 2.3-fold (90% CI [2.03-2.63]) and 1.6-fold (90% CI [1.42-1.84]) respectively. Since the interaction has not been established with dosages higher than 0,5 mg for repaglinide, the concomitant use of deferasirox with repaglinide should be avoided. If the combination appears necessary, a careful clinical and blood glucose monitoring should be performed (see section 4.4)". An interaction between EXJADE and other CYP2C8 substrates like paclitaxel cannot be excluded (see section 4.4).
IA/0013	IA_11_b_Change in batch size of active substance or intermediate - downscaling	24/09/2008	n/a		
IA/0012	IA_11_b_Change in batch size of active substance or intermediate - downscaling	24/09/2008	n/a		
IA/0011	IA_11_b_Change in batch size of active substance or intermediate - downscaling	24/09/2008	n/a		
IB/0008	IB_33_Minor change in the manufacture of the finished product	18/09/2008	n/a		
IB/0007	IB_41_a_02_Change in pack size - change in no. of units outside range of appr. pack size	05/09/2008	05/09/2008	SmPC, Labelling and PL	
IB/0006	IB_41_a_02_Change in pack size - change in no. of units outside range of appr. pack size	05/09/2008	05/09/2008	SmPC, Labelling and PL	
IB/0005	IB_41_a_02_Change in pack size - change in no. of units outside range of appr. pack size	05/09/2008	05/09/2008	SmPC, Labelling and	

				PL	
II/0003	Update of sections 4.2, 4.4, 4.5 and 4.8 of the SPC. The package leaflet is amended accordingly. Update of Summary of Product Characteristics and Package Leaflet	26/06/2008	25/07/2008	SmPC and PL	The MAH has applied upon request by CHMP following the assessment of the 4th PSUR, to add information regarding hepatic failure in section 4.4 and 4.8 and gastro-intestinal ulceration and haemorrhage in section 4.4 of the SPC. In addition, concomitant administration with substances of ulcerogenic potential and anti-coagulants is introduced in section 4.5. Further, the section 4.8 is updated with the ADRs "renal tubulopathy, gastrointestinal haemorrhage, gastric ulcer, duodenal ulcer, oesophagitis and hepatic failure". In addition, the MAH took the opportunity to add in section 4.5 of the SPC information on an interaction study with midazolam and to make editorial changes in section 4.2 regarding availability of strengths. The Package Leaflet is updated accordingly. Furthermore, some minor linguistic corrections to the Annexes in some languages are introduced. A Direct Health care professional communication agreed with CHMP was recommended to the applicant to inform the prescribers on new safety signals introduced in the SPC.
IA/0004	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	21/05/2008	n/a		
II/0002	The MAH has applied to add warning statements to section 4.4 of the SPC, to update the adverse drug reaction table in section 4.8 of the SPC with findings from the post-marketing setting, and to add information on cases of overdose to section 4.9 of the SPC. Furthermore, the MAH has made some minor linguistic corrections to the Annexes in some	24/05/2007	02/07/2007	SmPC, Annex II, Labelling and PL	Based upon data that have become available considers that the benefit-risk balance of Exjade remains positive. Changes were further made to the product information to bring it in line with the current EMEA/QRD template, SPC guideline and other relevant guideline(s), which were reviewed by QRD and accepted by the CHMP.

	languages and updated the Annexes according to the latest QRD template (version 7.2). Update of Summary of Product Characteristics, Labelling and Package Leaflet				
N/0001	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	02/03/2007	n/a	PL	