EMA/492188/2020

Yentreve

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
WS/1879	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. This worksharing variation is being submitted to present and discuss the results of Study F1J-MC-	03/09/2020	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).

	B034 Pregnancy Registry to meet the commitment made during the previous procedure No. EMEA/H/C/WS1527/G which received positive CHMP opinion on 25 July 2019. As a consequence of the submission of the F1J-MC-B034 Study Report, the Risk Management Plan (RMP) for duloxetine has been updated. The RMP for all Lilly duloxetine products are combined. The changes introduced are not specific to one product and are therefore the same for all products. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				
WS/1755	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. As agreed in the procedure WS-1527G in order to address the foetal outcomes, submission of the final report from study FIJ-MC-B059 'Observational Study to Assess Fetal Outcomes Following Maternal Exposure to Duloxetine' and the revised final report from study Study F1J-MC-B057 'Observational Studies to Assess Maternal and Fetal Outcomes Following Exposure to Duloxetine'. Section 4.6 of the SmPc and section 2 of the PL were	11/06/2020		SmPC and PL	As agreed in the procedure WS-1527G in order to address the foetal outcomes, submission of the final report from study FIJ-MC-B059 'Observational Study to Assess Fetal Outcomes Following Maternal Exposure to Duloxetine' and the revised final report from study Study F1J-MC-B057 'Observational Studies to Assess Maternal and Fetal Outcomes Following Exposure to Duloxetine'. Section 4.6 of the SmPc and section 2 of the PL were updated to reflect the available knowledge with regard to the usBe of duloxetine during pregnancy. The MAH took also the opportunity to include the declaration of sodium in the Product Information following

	updated to reflect the available knowledge with regard to the usBe of duloxetine during pregnancy. The MAH took also the opportunity to include the declaration of sodium in the Product Information following the guideline on 'Excipients in the labelling and package leaflet of medicinal products for human use'. During the assessment and following a transfer of MAH, Xeristar was removed from the WS procedure. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				the guideline on 'Excipients in the labelling and package leaflet of medicinal products for human use'. During the assessment and following a transfer of MAH, Xeristar was removed from the WS procedure.
IG/1134	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	14/08/2019	n/a		
IG/1126	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	25/07/2019	18/12/2019	SmPC and PL	
WS/1527/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.11.z (Type IB) - to stop enrolment of Study F1J-MC-B034 (study B034), another study included in the current EU-RMP as an additional pharmacovigilance	25/07/2019	18/12/2019	SmPC, Labelling and PL	Observational data have provided evidence of an increased risk (less than 2 -fold) of postpartum haemorrhage following duloxetine exposure within the month prior to birth. This risk is now reflected in the SmPC sections 4.4, 4.6 and 4.8.

	activities to address missing information regarding duloxetine exposure due to pregnancy. C.I.4 (Type II) - Update of sections 4.4, 4.6 and 4.8 of the SmPC in order to add a warning on the risk of postpartum haemorrhage based on final results from study Study F1J-MC-B057 listed as a category 3 in the RMP; this is an observational study to assess maternal and foetal outcomes following exposure to duloxetine. The Package Leaflet is updated accordingly. The RMP version 13 has also been submitted. In addition, the Worksharing applicant (WSA) took the opportunity to correct the term "sucrase-isomaltase" in section 4.4 of the SmPC in line with the Annex to the EC guideline on 'Excipients in the labelling and package leaflet of medicinal products for human use' (EMA/CHMP/302620/2017 corr. 1*) and to bring the PI in line with the latest QRD template version 10. The Xeristar 30 mg SmPC & Xeristar 60 mg SmPC and the Yentreve 20 mg SmPC & Yentreve 40 mg SmPC have been combined in a single SmPC, respectively, following the Policy on combined SmPCs (EMA/333423/2015). C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation				

WS/1598	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.3.b - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a procedure concerning PSUR or PASS or the outcome of the assessment done under A 45/46 - Change(s) with new additional data submitted by the MAH	14/06/2019	18/12/2019	SmPC	
WS/1619	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	06/06/2019	n/a		
IG/1055	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	18/01/2019	18/12/2019	SmPC and PL	
IG/0996	A.7 - Administrative change - Deletion of manufacturing sites	23/10/2018	n/a		
PSUSA/1187/ 201708	Periodic Safety Update EU Single assessment - duloxetine	12/04/2018	n/a		PRAC Recommendation - maintenance
WS/1264	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.	08/02/2018	n/a		The association between suicide attempts and receipt of duloxetine treatment in women with stress urinary inconsistence (SUI) compared to women with SUI without duloxetine treatment has been assessed in study F1J-MC-

	Submission of the final report from study F1J-MC-B056 listed as a category 3 study in the RMP. This is a non-interventional non-imposed study aimed to investigate the association between duloxetine exposure and suicide-related behaviours and ideation in women with stress urinary inconsistence (SUI). The RMP version 12.4 has also been updated to reflect the study results. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				B056. Study B056 has several limitations but in the light of the results the association between the risk of suicidality and duloxetine treatment cannot be completely ruled out. Currently, the risk of suicidality is an important identified risk for duloxetine-containing products and adequate warnings concerning this risk are already included in the SmPC. No further changes to the product information are warranted. The RMP is updated to reflect the study results and limitations and update the pharmacovigilance plan regarding this study.
IG/0759/G	This was an application for a group of variations. B.III.1.b.2 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer B.III.1.b.2 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved manufacturer B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved	11/01/2017	n/a		

	manufacturer B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved manufacturer				
N/0056	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	09/12/2016	18/12/2019	Labelling	
WS/1015	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. To update the RMP to add a new Observational Study to Assess Maternal and Fetal Outcomes Following Exposure to Duloxetine (F1J-MC-B057), and to update the plans for the existing pregnancy registry (F1JMC-B034) in section III.4.3 of 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 change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required	13/10/2016	n/a		
IG/0664	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	25/02/2016	n/a		

IG/0662	A.1 - Administrative change - Change in the name and/or address of the MAH	23/02/2016	30/06/2016	SmPC, Labelling and PL	
WS/0758	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of section 4.8 of the SmPC in order to add microscopic colitis with frequency category 'rare' as a new ADR identified from post marketing experience. The Package Leaflet is updated accordingly. In addition, the Worksharing applicant took the opportunity to make minor editorial changes in the SmPC and PL and to update the local representative for Italy in the Package Leaflet for Xeristar. Moreover, the Worksharing applicant took the opportunity to correct the stated mass of sucrose in capsule in section 2 of the SmPC. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	09/07/2015	30/06/2016	SmPC and PL	
PSUSA/1187/ 201408	Periodic Safety Update EU Single assessment - duloxetine	26/03/2015	27/05/2015	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/1187/201408.
IG/0472	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	18/08/2014	n/a		

IG/0457/G	This was an application for a group of variations. B.III.1.b.2 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer B.III.1.b.2 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer B.III.1.b.2 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer B.III.1.b.2 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer B.III.1.b.2 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer B.III.1.b.2 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer	14/07/2014	n/a		

	B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved manufacturer B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved manufacturer B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved manufacturer B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved manufacturer B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved manufacturer B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved manufacturer B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved manufacturer B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved manufacturer				

IB/0048/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	03/02/2014	n/a		
IG/0383	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	06/12/2013	n/a		
WS/0444	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of sections 4.4 and 4.5 of the SmPC to introduce a description of the signs and symptoms of 'serotonin syndrome' and provided an updated list of examples of MAOIs and serotonergic agents. These changes have been proposed by PRAC and endorsed by the CHMP. The Package Leaflet was updated accordingly. C.I.z - Changes (Safety/Efficacy) of Human and	24/10/2013	08/10/2014	SmPC and PL	This variation updated the product information with details of a condition called serotonin syndrome which may occur when medicines acting on the serotonin system in the brain are given concomitantly. Examples of such medicines have been also provided and included in the product information. These changes have been proposed by Pharmacovigilance Risk Assessment Committee (PRAC) and endorsed by the Committee for Medicinal Products for Human Use (CHMP).

	Veterinary Medicinal Products - Other variation				
IG/0321	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	17/07/2013	n/a		
WS/0334/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Scope (Ariclaim) The variations introduced several updates to different sections of the SmPCs of Ariclaim, Cymbalta Xeristar and Yentreve, following the assessment of the data acquired form the performed database analysis of observed ADRs, and the data from the performed two studies in the paediatric population. The changes were specific for the different products, according to the indications they were licensed for. For Ariclaim the updates included: Update to sections 4.4, 4.8 of the SmPC in order to remove the statement that no clinical trials have been conducted in paediatric population, to add the adverse events (AEs) 'dysphagia' and 'pollakiuria', and to update the description of sensory disturbances as requested by the CHMP further to the assessment of PSUR 11. Update of section 4.8 of the SmPC to add the AE 'testicular pain' and to reflect the increased reporting frequency of the adverse event 'falls'. Update to the list of the most commonly reported discontinuation symptoms in Section	30/05/2013	01/07/2013	SmPC, Annex II and PL	The MAH conducted an updated review of ADR. As a result of this analysis a number of changes to the PI were introduced. The following new ADRs were added to section 4.8 of the SmPC: 'dysphagia', 'testicular pain' (not relevant for YENTREVE) and 'pollakiuria'. The frequency for the ADR 'falls' was also updated. Additionally, the MAH updated the list of most commonly reported discontinuation symptoms to include "myalgia". The term "sensory disturbances (including paresthesia)" was changed to "sensory disturbances (including paresthesia or electric shock-like sensations, particularly in the head)". Additionally, the data from two completed studies of duloxetine in paediatric patients with major depressive disorder were available for analysis and resulted in a number of other changes to the PI. The wording of Section 4.2 – Posology and Method of Administration, describing the fact that duloxetine should not be used in children and adolescents was updated to read: "Duloxetine should not be used in children and adolescents under the age of 18 years for the treatment of major depressive disorder because of safety and efficacy concerns".

	4.8c:'Description of selected adverse reactions' to include the term 'myalgia' and update the term 'sensory disturbances (including paraesthesia or electric shock-like sensations, particularly in the head)' as requested by the CHMP further to the assessment of the cumulative review of the cases with "electric shock-like sensations". Furthermore, the MAH used the opportunity to bring the PI in line with the QRD template version 8.3. The Package Leaflet was updated accordingly. Scope (Cymbalta) The variations introduced several updates to different sections of the SmPCs of Ariclaim, Cymbalta Xeristar and Yentreve, following the assessment of the data acquired form the performed database analysis of observed ADRs, and the data from the performed two studies in the paediatric population. The changes were specific for the different products, according to the indications they were licensed for. For Cymbalta the updates included: Update to sections 4.4, 4.8 of the SmPC in order to remove the statement that no clinical trials have been conducted in paediatric population, to add the adverse events (AEs) 'dysphagia' and 'pollakiuria', and to update the description of sensory disturbances as requested by the CHMP further to the assessment of PSUR 11. Update of section 4.8 of the SmPCs, to add the AE 'testicular pain' and to reflect the increased reporting frequency of the adverse event 'falls'. Update to the list of the most commonly reported				

	discontinuation symptoms in Section 4.8c:'Description of selected adverse reactions' to include the term 'myalgia' and update the term 'sensory disturbances (including paraesthesia or electric shock-like sensations, particularly in the head)' as requested by the CHMP further to the assessment of the cumulative review of the cases with "electric shock-like sensations". Update of sections 4.2, 4.8 and 5.1 with text reflecting the results of two placebo-controlled trials with 800 paediatric major depressive disorder (MDD) patients. Furthermore, the MAH used the opportunity to bring the PI in line with the QRD template version 8.3. The Package Leaflet was updated accordingly. Scope (Xeristar) The variations introduced several updates to different sections of the SmPCs of Ariclaim, Cymbalta Xeristar and Yentreve, following the assessment of the data acquired form the performed database analysis of observed ADRs, and the data from the performed two studies in the paediatric population. The changes were specific for the different products, according to the indications they were licensed for. For Xeristar the updates included: Update to sections 4.4, 4.8 of the SmPC in order to remove the statement that no clinical trials have been conducted in paediatric population, to add the adverse events (AEs) 'dysphagia' and 'pollakiuria', and to update the description of sensory disturbances as requested by the CHMP further to				

	the assessment of PSUR 11. Update of section 4.8 of the SmPC, to add the AE 'testicular pain' and to reflect the increased reporting frequency of the adverse event 'falls'. Update to the list of the most commonly reported discontinuation symptoms in Section 4.8c:'Description of selected adverse reactions' to include the term 'myalgia' and update the term 'sensory disturbances (including paraesthesia or electric shock-like sensations, particularly in the head)' as requested by the CHMP further to the assessment of the cumulative review of the cases with "electric shock-like sensations". Update of sections 4.2, 4.8 and 5.1 with the results of two placebo-controlled trials with 800 paediatric major depressive disorder (MDD) patients. Furthermore, the MAH used the opportunity to bring the PI in line with the QRD template version 8.3. The Package Leaflet was updated accordingly. Scope (Yentreve) The variations introduced several updates to different sections of the SmPCs of Ariclaim, Cymbalta Xeristar and Yentreve, following the assessment of the data acquired form the performed database analysis of observed ADRs, and the data from the performed two studies in the paediatric population. The changes were specific for the different products, according to the indications they were licensed for. For Yentreve the updates included: Update to sections 4.4, 4.8 of the SmPC in order to remove the statement that no clinical trials have				

	been conducted in paediatric population, to add the adverse events (AEs) 'dysphagia' and 'pollakiuria', and to update the description of sensory disturbances as requested by the CHMP further to the assessment of PSUR 11. Update to the list of the most commonly reported discontinuation symptoms in Section 4.8c:'Description of selected adverse reactions' to include the term 'myalgia' and update the term 'sensory disturbances (including paraesthesia or electric shock-like sensations, particularly in the head)' as requested by the CHMP further to the assessment of the cumulative review of the cases with "electric shock-like sensations". Furthermore, the MAH used the opportunity to bring the PI in line with the QRD template version 8.3. The Package Leaflet was updated accordingly. 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 C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				
IG/0239	B.III.2.a.1 - Change of specification('s) of a former non Pharmacopoeial substance to comply with the Ph. Eur. or with a national pharmacopoeia of a Member State - AS	28/11/2012	n/a		

IG/0178	A.7 - Administrative change - Deletion of manufacturing sites	11/05/2012	n/a		
WS/0181/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Changes in testing of the active substance 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.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	17/11/2011	17/11/2011		
WS/0135	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. This variation application followed a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008 and concerned: - Update of the SmPC section 4.4 to include NSAIDS and ASA as examples of antiplatelet agents. - Update of the SmPC section 4.8 to include terms	23/06/2011	27/07/2011	SmPC and PL	In this variation sections of the product information which provide information on precautions one should take before taking duloxetines were updated with examples of medicines that prevent the blood from clotting, e.g. non steroidal anti-inflammatory drugs and acetylsalicylic acid. New information was also added to the sections of the product information describing possible side effects, for example: menstrual disorder, increase in blood potassium levels, dry eye and falls. Somnolence was added to the list of most commonly reported withdrawal symptoms. It was

	'menstrual disorder', 'blood potassium increased', 'dry eye' and 'falls' to the tabulated summary of adverse reactions and to add 'somnolence' to the list of most commonly reported withdrawal symptoms. A footnote "falls were more common in the elderly (more than 65 years old)" was added to 'falls'. Additionally frequencies of some currently listed ADRs were changed. These updates were based on the most recent CCDS from February 2011. The Package Leaflet has been updated accordingly. Furthermore, minor editorial changes were also introduced to the product information. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				also mentioned that the patients older than 65 years might experience falls more often. In addition, frequencies of several side effects were updated.
IA/0036/G	This was an application for a group of variations. C.I.9.i - Changes to an existing pharmacovigilance system as described in the DDPS - Change(s) to a DDPS following the assessment of the same DDPS in relation to another medicinal product of the same MAH 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	28/02/2011	n/a		

WS/0071	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	16/12/2010	21/01/2011	SmPC, Annex II, Labelling and PL	This variation updates the SmPC section 4.4 with the laboratory measure of the seriousness of low sodium levels in blood and underlines the fact that the elderly are at risk of low sodium levels. The Package Leaflet has been updated accordingly. Additionally, the contact details for the local representatives in Estonia for the Ariclaim, Cymbalta, Xeristar and Yentreve Package Leaflets have been updated.
IG/0031	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	17/12/2010	n/a		
WS/0011/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation 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	22/07/2010	31/08/2010	SmPC and PL	This application was submitted for a group of variations consisting of two type 1B variations. In the variation C.I.z the MAH updated the section 4.6 'Pregnancy and lactation' of the SmPC with symptoms and time to onset of neonatal drug withdrawal syndrome and added galactorrhoea and hyperprolactinaemia to section 4.8 'Undesirable effects' of the SmPC as the result of the assessment of PSUR-9. The Package Leaflet has been updated accordingly. In the variation C.I.3.a the MAH updated the section 'Pregnancy and lactation' of the Product Information following the class review for SSRIs/SNRIs to inform that when taken during pregnancy SSRI/SNRIs may increase the risk of persistent pulmonary hypertension in neonates. In addition the MAH introduced minor administrative, editorial and linguistic changes to the Product Information.
II/0035	Update of section 4.5 of the Summary of Product Characteristics to reflect the results of a recent	29/05/2009	07/07/2009	SmPC	Study F1J-MC-HMFP was an open-label study with the primary objective to evaluate the anticoagulant effects of

	duloxetine/warfarin interaction study (study F1J-MC-HMFP). Furthermore, the term "adolescents" was included in section 4.2 of the SPC in order to align this section with the current QRD template. Update of Summary of Product Characteristics				multiple doses of warfarin when taken at the same time with multiple doses of duloxetine as measured by changes in the international normalized ratio (INR). Increases in INR values were reported when duloxetine was co-administered with warfarin. However, concomitant administration of duloxetine with warfarin under steady state conditions, in healthy volunteers, as part of a clinical pharmacology study, did not result in a clinically significant change in INR from baseline or in the pharmacokinetics of warfarin.
R/0032	Renewal of the marketing authorisation.	23/04/2009	24/06/2009	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 Yentreve continues to be favourable. The MAH will continue to submit a yearly PSUR.
II/0034	to change the finished product specification. Quality changes	23/04/2009	12/05/2009		
II/0031	Update of Summary of Product Characteristics and Package Leaflet	19/02/2009	03/04/2009	SmPC and PL	
IA/0033	IA_38_a_Change in test procedure of finished product - minor change to approved test procedure	24/02/2009	n/a		
IB/0029	IB_13_b_Change in test proc. for active substance - other changes (replacement/addition)	31/07/2008	n/a		

IB/0030	IB_33_Minor change in the manufacture of the finished product	24/07/2008	n/a		
IB/0028	IB_18_Replacement of an excipient with a comparable excipient	07/07/2008	n/a		
II/0026	Update of Summary of Product Characteristics sections 4.4, 4.8, 4.9 and 4.6. The Package Leaflet has been updated accordingly to reflect the changes. The Product Information has been updated according to the latest QRD Template. Update of Summary of Product Characteristics, Labelling and Package Leaflet	19/03/2008	23/04/2008	SmPC, Labelling and PL	The MAH following a search in their in-house clinical trial database as well as the post-marketing data from the spontaneous reporting has applied for changes in the section 4.8 "Undesirable effects" with the inclusion of new adverse drug reactions ("tinnitus", "gait disturbance", "poor quality sleep", "polyuria", "urine flow decreased", "sexual dysfunction" and "dermatitis contact") as well with the modification of the frequency in already known ones. In addition the cases for overdose have been reviewed and the wording has been modified in section 4.9 "Overdose" to include "coma" and "tachycardia" as symptoms of overdosing. The text was also amended to include signs and symptoms of overdosing observed with duloxetine alone or in combination with other medicinal products. The section 4.6 "Pregnancy and lactation" of the SPC has been harmonised for all duloxetine containing products. The section 4.4 of the SPC has been updated to include information on possible side effects in case of co-administration of St John wort. The Package Leaflet has been updated to include the relevant information corresponding to the changes in the SPC. The Product Information has been updated to include

					editorial changes according to the latest QRD Template. The local representatives of Latvia and Slovenia have been updated.
IA/0027	IA_22_a_Submission of TSE Ph. Eur. certificate for exc. - Approved/new manufacturer	31/01/2008	n/a		
IB/0025	IB_10_Minor change in the manufacturing process of the active substance	05/12/2007	n/a		
IB/0024	IB_30_b_Change in supplier of packaging components - replacement/addition	30/08/2007	n/a		
II/0022	Update of section 4.8 of the Summary of Product Characteristics (SPC) regarding gastrointestinal bleedings and withdrawal symptoms, section 4.9 of the SPC regarding dosing and as requested by the CHMP and following discussions at the PhVWP to also update the wording on suicidality in section 4.4 of the SPC. The relevant sections of the Package Leaflet (PL) are amended accordingly. Update of Summary of Product Characteristics and Package Leaflet	19/07/2007	28/08/2007	SmPC and PL	Following the PSUR 4 (covering period 3 February 2006 to 2 August 2006) the MAH was requested to update the Product Information with the latest undesirable effects as well as the dosing of the product. In addition and following a meta-analysis published by the FDA regarding the suicidality of the patients administered duloxetine and further to scientific discussions at the PhVWP in June 2007 re-wording of that information has been performed in the section 4.4 of the SPC.
IB/0020	IB_12_b_02_Change in spec. of active subst./agent in manuf. of active subst. - test parameter	08/06/2007	n/a		
IB/0023	IB_14_b_Change in manuf. of active substance without Ph. Eur. certificate - new manufacturer	24/05/2007	n/a		

IA/0021	IA_11_b_Change in batch size of active substance or intermediate - downscaling	29/03/2007	n/a		
N/0018	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	08/03/2007	n/a	PL	
II/0016	The Marketing Authorisation Holder applied for an update of the Summary of Product Charasteristics (SPC) and the Package Leaflet (PL) following the review of the 3rd PSUR and review of duloxetine placebo-controlled clinical trial database. Sections 4.3, 4.4, 4.5, 4.6, 4.8, and 4.9 of the SPC and sections 2 and 4 of the PL have been amended. Update of Summary of Product Characteristics and Package Leaflet	18/10/2006	28/11/2006	SmPC and PL	Following the assessment of the third Periodic Safety Update Report (PSUR) the CHMP requested to the MAH to submit a variation to reflect the new safety information. In addition, the MAH also proposed some changes to the SPC following the review of the placebo-controlled clinical trial database. In this variation, the following sections have been updated: Section 4.3 - Contraindications Addition of contraindication with regards to the initiation of treatment in patients with uncontrolled hypertension. Section 4.4. Special warning and precautions of use In this variation warnings have been included in this section: -to update information on extrapyramidal disorders -to update information on blood pressure and heart rate. Section 4.5 Interaction with other medicinal products and other forms of interactions This section was updated to state that ''Caution should be exercised when duloxetine is combined with oral anticoagulants or antiplatelets drugs due to an increased risk of bleeding. Furthermore, increases in INR values have been reported when duloxetine was co-administered with warfarin". In addition to this, the following information has

					been included: Duloxetine is an inhibitor of CYP2D6 and therefore caution is advised when duloxetine is co-administered with medicinal products predominantly metabolised by this route (i.e. risperidone, tricyclic antidepressants such as nortriptyline, amitriptyline, and imipramine). Section 4.6 Pregnancy and Lactation Section 4.6 was updated to reflect that duloxetine is very weakly excreted into human milk based on a study of 6 lactating patients. Section 4.8 Undesirable effects The following Adverse Drug Reactions (ADRs) have been included in the section 4.8: Hypertensive crisis, supraventricular arrhythmia mainly, atrial fibrillation, paresthesia, hepatic failure, trismus, mania. In addition to this, the MAH updated the frequency of ADRs in section 4.8 to reflect the most recent clinical trials data.
IA/0017	IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size	04/09/2006	04/09/2006	SmPC, Labelling and PL	
II/0015	Change(s) to the manufacturing process for the active substance	27/07/2006	03/08/2006		
II/0012	The Marketing Authorisation Holder (MAH) applied for an update of the Summary of Product Characteristics (SPC) and Package Leaflet (PL) to include new safety information following the review of the 2nd PSUR and results from a pharmacokinetic study in lactating women. Additional sections in the	27/04/2006	31/05/2006	SmPC, Annex II, Labelling and PL	Following the assessment of the second Periodic Safety Update Report (PSUR) the CHMP identified a number of adverse reactions clinical relevant and which were not yet reflected in the Product Information. Therefore the MAH was requested to submit a variation to reflect the new safety information. In this variation warnings have been

	SPC and PL have been amended. Update of Summary of Product Characteristics, Labelling and Package Leaflet				included in section 4.4 of the SPC: - to recommend caution in patients whose conditions could be compromised by an increased heart rate or by an increase in blood pressure - to update information on withdrawal syndrome seen on discontinuation of treatment - to update information on extrapiramidal disorders Section 4.8 (Undesirable Effects) of the SPC was also updated with regards to withdrawal symptoms and on the effects of duloxetine in Hb1Ac. In addition, the following ADRs have been added to section 4.8: chest pain, seizures, hypertension, hallucinations, akathisia, psychomotor restlessness Section 4.5 of the SPC (Interaction with other medicinal products) was updated to state that "Increases in INR have been reported when duloxetine was co-administered with warfarin" and to include some examples of drugs metabolised by CYP2D6 with a narrow therapeutic range (such as flecainide, propafenone and metoprolol) in which case caution is advised if Yentreve is co-administered. In this variation the MAH also update sections 4.6 and 5.2 of the SPC to reflect the results of a pharmacokinetic study in lactating women. The Package Leaflet was updated to reflect the above changes.
N/0014	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	12/05/2006	n/a	PL	

IA/0013	IA_08_a_Change in BR/QC testing - repl./add. of batch control/testing site	19/04/2006	n/a		
II/0009	This variation relates to an update of sections 4.4 and 4.8 of the SPC with safety information following assessment of PSUR 1 and a minor addition to section 4.7 concerning the potential for dizziness, with consequential changes to the relevant sections of the PL. Update of Summary of Product Characteristics and Package Leaflet	23/02/2006	29/03/2006	SmPC and PL	The MAH has updated the SPC and PL with safety information following assessment of the first Periodic Safety Update Report (PSUR). During the assessment of PSUR 1, 3 cases of SIADH (Severe Inappropriate Anti-Diuretic Hormone secretion), 7 cases of hyponatremia and 7 cases of blood sodium decreased were reported. These cases involved elderly patients (mean 76 years). In a number of cases risk factors were identified (pre-existing low level of blood sodium, renal failure, concomitant treatment with ACE or diuretics). Information has been added to section 4.4 of the SPC on that caution is required in patients at increased risk of hyponatraemia such as elderly, cirrhotic, or dehydrated patients or patients treated with diuretics. Hyponatraemia may reflect a syndrome of inappropriate anti-diuretic hormone secretion (SIADH). During the assessment of PSUR 1, 12 cases of gastrointestinal bleeding were reported. In a number of cases risk factors were identified. Nevertheless, there are a number of epidemiological studies showing that drugs that inhibit 5HT re-uptake increase the risk of bleeding, including gastrointestinal bleeding. Information has been added to section 4.4 of the SPC on that reports of gastrointestinal haemorrhage has been seen. As an increase in approximately 2 mmHg mean increase in blood pressure has been seen in patients treated with

					duloxetine, information is added to section 4.4 of the SPC on that duloxetine is associated with an increase in blood pressure in some patients. In patients with known hypertension and/or other cardiac disease, blood pressure monitoring is recommended as appropriate.Cases of liver injury, including severe elevations of liver enzymes (>10 times upper limit of normal), hepatitis and jaundice have been reported with duloxetine (see section 4.8). The pattern of liver damage was predominantly hepatocellular. This information was included in the SPC and it was recommended that duloxetine should be used with caution in pa
II/0010	Update of sections 4.4 and 4.5 of the SPC with consequent amendments to the PL, following review of suicidal attempts. Update of Summary of Product Characteristics and Package Leaflet	13/10/2005	17/11/2005	SmPC and PL	The SPC was updated to include additional information on suicidal ideation, suicidal behaviour as well as any concomitant use with antidepressants following the CHMP's review of data available regarding suicide attempts in the approved indication. It was concluded that if the patient develops depressive symptoms while on Yentreve therapy, specialised medical advice should be sought and if a decision to start treatment with antidepressants are taken, treatment with Yentreve should gradually be stopped. Further, the use of Yentreve in combination with antidepressants (especially with SSRI, SNRI and reversible MAOIs) is not recommended.
II/0006	Update of the section 4.4. of the SPC to add a warning regarding concomitant use of duloxetine-containing products, to section 4.8 to add information regarding increased fasting blood glucose and to section 5.1 to include the final ATC code approved by the WHO (Other antidepressants N06AX21). The PL was amended accordingly.	27/07/2005	19/09/2005	SmPC and PL	The SPC was updated to state that different trademarks are used for duloxetine-containing products authorised in several indications (treatment of diabetic neuropathic pain, major depressive episodes as well as stress urinary incontinence) and that the use of more than one of these products concomitantly should be avoided. Information was included on that a in clinical trials of duloxetine in patients

	Update of Summary of Product Characteristics and Package Leaflet				with diabetic neuropathic pain, small but statistically significant increases in fasting blood glucose were observed in duloxetine-treated patients compared to placebo at 12 weeks and routine care at 52 weeks. The increase was similar at both time points and was not considered clinically relevant. Relative to placebo or routine care, mean HbA1c values were stable, there was no mean weight gain, mean lipid concentrations (cholesterol, LDL, HDL, triglycerides) were stable, and there were no differences in incidence of serious and non-serious diabetes-related adverse reactions.
II/0005	Update of the section 4.2 of the SPC in order to optimise the wording on starting dose recommendations with consequential changes to the section 3 of the PL. Update of Summary of Product Characteristics and Package Leaflet	27/07/2005	19/09/2005	SmPC and PL	Based on a study evaluating the effect of three different dosing regimens on the most prevalent treatment-emergent-adverse-event nausea, the SPC was updated to state that some patients may benefit from starting treatment at a dose of 20 mg twice daily for two weeks before increasing to the recommended dose of 40 mg twice daily. Dose escalation may decrease, though not eliminate, the risk of nausea and dizziness. However, limited data are available to support the efficacy of YENTREVE 20 mg twice daily.
A18/0011	Procedure under Article 18 of Council Regulation (EEC) No. 2309/93, as amended, to review suicide-related behaviours in children and adolescents. Article 18 Review	23/06/2005	15/09/2005	SmPC and PL	Please refer to Scientific Conclusion Yentreve-EMEA/H/A-18/652
IB/0008	IB_38_c_Change in test procedure of finished product - other changes	19/07/2005	n/a		
IB/0007	IB_38_c_Change in test procedure of finished product - other changes	19/07/2005	n/a		

IB/0004	IB_42_a_01_Change in shelf-life of finished product - as packaged for sale	26/05/2005	n/a	SmPC	
IA/0003	IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size	28/04/2005	28/04/2005	SmPC, Labelling and PL	
IA/0002	IA_22_a_Submission of TSE Ph. Eur. certificate for exc. - Approved/new manufacturer	29/03/2005	n/a		
IB/0001	IA_08_a_Change in BR/QC testing - repl./add. of batch control/testing site IB_07_c_Replacement/add. of manufacturing site: All other manufacturing operations ex. batch release	15/12/2004	n/a		