Aloxi

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
II/0045/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites B.II.a.1.a - Change or addition of imprints, bossing or other markings including replacement, or addition of inks used for product marking - Changes in	22/03/2018	26/04/2018	SmPC, Annex II, Labelling and PL	Update of sections 2, 3 and 6.1 of the SmPC for Aloxi 500 micrograms soft capsules to reflect the deletion of the printing ink from the capsule and the reduction in the amount of sorbitol in the capsule shell, due to the reduction in size of the capsule shell. The package leaflet (PL) is updated accordingly. The PI is brought in line with the current QRD template version 10, the SmPC is updated to align with the numbering in Annex A and the PL has been aligned with the

[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).

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5520
Send a question via our website www.ema.europa.eu/contact

	imprints, bossing or other markings B.II.a.2.a - Change in the shape or dimensions of the pharmaceutical form - Immediate release tablets, capsules, suppositories and pessaries B.II.a.3.b.5 - Changes in the composition (excipients) of the finished product - Other excipients - Change that is supported by a bioequivalence study B.II.b.1.e - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non-sterile medicinal products B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place B.II.b.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 B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.4.a - Change in the batch size (including batch size ranges) of the finished product - Up to 10-fold compared to the originally approved batch size B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished				updated excipients guideline (EMA/CHMP/302620/2017). Changes to the PL arising from User testing assessment are implemented. Finally, Annex II of Aloxi 250 microgram solution for injection is aligned with the SmPC.

	product - Other variation B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation B.II.d.2.z - Change in test procedure for the finished product - Other variation				
IA/0046/G	This was an application for a group of variations. A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release) B.II.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	26/03/2018	n/a		
IA/0044/G	This was an application for a group of variations. A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release) B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	05/04/2017	n/a		
PSUSA/2268/ 201607	Periodic Safety Update EU Single assessment - palonosetron	09/03/2017	n/a		PRAC Recommendation - maintenance

IB/0042/G	This was an application for a group of variations. B.II.b.1.e - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non-sterile medicinal products B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place B.II.c.1.g - Change in the specification parameters and/or limits of an excipient - Where there is no monograph in the European/National Ph. for the excipient, a change in specification from in-house to a non-official/third country Ph. B.II.c.2.a - Change in test procedure for an excipient - Minor changes to an approved test procedure B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	01/08/2016	n/a		
IA/0041/G	This was an application for a group of variations. B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor	31/03/2016	n/a		

	changes to an approved test procedure B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.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				
II/0040	B.I.a.1.b - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Introduction of a manufacturer of the AS supported by an ASMF	18/02/2016	n/a		
II/0038	Extension of Indication for the Aloxi IV formulation to include paediatric patients 1 month of age and older for the prevention of acute nausea and vomiting associated with highly emetogenic cancer chemotherapy and prevention of nausea and vomiting associated with moderately emetogenic cancer chemotherapy. As a consequence, update of sections 4.1, 4.2, 4.8, 4.9, 5.1 and 5.2 of the SmPC. The Package Leaflet is updated in accordance. Sections 5.1 and 5.2 of the SmPC of the Aloxi Oral formulation were updated to reflect the studies. Furthermore, the PI is being brought in line with the latest QRD template version 9.0. The requested variation proposed amendments to the SmPC, Labelling and Package Leaflet.	22/01/2015	24/02/2015	SmPC and PL	Please refer to the scientific discussion Aloxi EMEA/H/C/000563/II/38 for further information.

	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
IB/0039/G	This was an application for a group of variations. B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation B.II.f.1.b.1 - Stability of FP - Extension of the shelf life of the finished product - As packaged for sale (supported by real time data)	19/12/2014	24/02/2015	SmPC	
IA/0037/G	This was an application for a group of variations. B.III.1.b.4 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Deletion of certificates (in case multiple certificates exist per material) 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	28/04/2014	n/a		
IAIN/0036/G	This was an application for a group of variations. B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	25/04/2014	n/a		

	B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place B.II.c.1.z - Change in the specification parameters and/or limits of an excipient - Other variation B.II.c.2.a - Change in test procedure for an excipient - Minor changes to an approved test procedure B.II.c.1.b - Change in the specification parameters and/or limits of an excipient - Addition of a new specification parameter to the specification with its corresponding test method B.II.c.z - Change in control of excipients in the Finished Product - Other variation C.I.8.a - Introduction of or changes to a summary of Pharmacovigilance system - Changes in QPPV (including contact details) and/or changes in the PSMF location B.II.c.1.b - Change in the specification parameters and/or limits of an excipient - Addition of a new specification parameter to the specification with its corresponding test method 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				
PSUV/0033	Periodic Safety Update	20/02/2014	23/04/2014	SmPC and PL	Please refer to Aloxi-H-C-563-PSUV-0033 EPAR: Scientific conclusions and grounds recommending the variation to the terms of the marketing authorisation.
IB/0035	C.I.11.z - Introduction of, or change(s) to, the	13/12/2013	n/a		

	obligations and conditions of a marketing authorisation, including the RMP - Other variation				
N/0034	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	13/12/2013	23/04/2014	PL	
IA/0032	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	25/06/2013	n/a		
IA/0031/G	This was an application for a group of variations. 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 A.7 - Administrative change - Deletion of manufacturing sites	23/04/2013	n/a		
IAIN/0030/G	This was an application for a group of variations. C.I.9.a - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the QPPV C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system	13/08/2012	n/a		
IA/0029	A.7 - Administrative change - Deletion of manufacturing sites	03/07/2012	n/a		

IA/0028/G	This was an application for a group of variations. 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 A.5.b - Administrative change - Change in the name and/or address of a manufacturer of the finished product, including quality control sites (excluding manufacturer for batch release) B.II.e.2.c - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	27/04/2012	n/a		
II/0027	Update of section 4.2 of the Aloxi Oral SmPC in order to remove the sentence “This medicinal product should be administered by a healthcare professional under appropriate medical supervision.” The Package Leaflet is updated in accordance. Furthermore the DDPS version number was deleted from Annex II B. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	19/01/2012	21/02/2012	SmPC, Annex II and PL	CINV can occur the day of chemotherapy and up to 5 days later. Oncology patients usually continue self administering antiemetic medications to prevent CINV. Given the well-established and favourable safety profile of Aloxi, and to be consistent with current medical practice for patient self-medication to prevent CINV, and further recognizing that the SmPCs for other oral 5-HT3 licensed for prevention of CINV allow patient self-medication, the requirement that Aloxi capsules are to be administered by healthcare professionals can be omitted.

					As Aloxi is under prescription control it is taken in accordance with instructions as indicated by the physician. Should the treating physician have any specific concerns whether self-administration of Aloxi capsules is not appropriate for a given patient this might be addressed by the physician on a case by case basis.
IA/0026/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 supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS 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 B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.I.c.1.a - Change in immediate packaging of the AS - Qualitative and/or quantitative composition	04/05/2011	n/a		
II/0025	Update of section 4.2, 5.1 and 5.2 of the SmPC to include information from paediatric studies PALO-99-07 and PALO-07-29 following A 46 procedure. Furthermore, editorial changes have been made in sections 8, 9 and 10 of the SmPC, Annex II and Package Leaflet. C.I.3.b - Implementation of change(s) requested	18/11/2010	20/12/2010	SmPC, Annex II and PL	The MAH has conducted two paediatric Phase 3 studies to evaluate the safety and efficacy of Aloxi 250 mcg solution for injection in paediatric patients with CINV (PALO-99-07) and PONV (PALO-07-29), respectively. In addition, study PALO-99-07 also assessed the pharmacokinetic properties of two doses of IV palonosetron in the paediatric population. While Aloxi is not recommended for the use in children below age 18 due to insufficient data, in

	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				accordance with the current Guideline on Summary of Product Characteristics, the available information in the paediatric population has been summarized in sections 5.1 and 5.2 of the SmPC.
IB/0024	B.I.a.2.e - Changes in the manufacturing process of the AS - Minor change to the restricted part of an ASMF	18/10/2010	n/a		
N/0023	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	15/07/2010	n/a	Labelling and PL	
X/0015	Annex I_2.(d) Change or addition of a new pharmaceutical form	21/01/2010	05/05/2010	SmPC, Annex II, Labelling and PL	Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Aloxi 500 microgram capsule in the prevention of nausea and vomiting associated with moderately emetogenic cancer chemotherapy was favourable and therefore recommended the granting of the marketing authorisation.
R/0020	Renewal of the marketing authorisation.	17/12/2009	23/03/2010	SmPC, Annex II, Labelling and PL	Based on the CHMP review of the available information and on the basis of a re-evaluation of the benefit risk balance, the CHMP is of the opinion that the quality, safety and efficacy of this medicinal product continues to be adequately and sufficiently demonstrated and therefore considered that the benefit risk profile of Aloxi continues to be favourable. The CHMP recommends the renewal of the Marketing Authorisation with unlimited validity.
IB/0022	B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of	05/03/2010	n/a		

	specification limits				
II/0019	Addition of an alternative manufacturer of a bulk product and primary packaging site with consequential changes to the manufacturing process of the finished product. Quality changes	19/11/2009	25/11/2009		
IB/0021	IB_07_c_Replacement/add. of manufacturing site: All other manufacturing operations ex. batch release	24/09/2009	n/a		
IB/0017	IB_42_a_01_Change in shelf-life of finished product - as packaged for sale	29/05/2009	n/a	SmPC	
N/0016	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	23/04/2009	n/a	PL	
II/0013	Update of SPC sections 4.4 and 5.1 to include additional information pertinent to the warning on QT/QTc prolongation mainly based on results of clinical study. In addition, the PL section 2 has been amended with information regarding personal of family history of QT prolongation. Update of Summary of Product Characteristics and Package Leaflet	18/12/2008	29/01/2009	SmPC and PL	The update of SPC sections 4.4 and 5.1 was mainly based on a phase 1, randomised, single dose, double-blind, double dummy, parallel group, placebo-controlled and active comparator study demonstrating that there were no dose-related ECG effects of single doses of palonosetron from 0.25 to 2.25 mg covering a 9-fold range of exposure (where the lower limit is the current recommended dose of palonosetron for single day chemotherapy). Out of 221 subjects, 42 were with placebo, 44 with palonosetron 0.25 mg IV, 46 with palonosetron 0.75 mg IV, 46 with palonosetron 2.25 mg IV and 43 with moxifloxacin 400 mg oral. The upper boundary of the one-sided 95% confidence interval for all time points for all 3 doses of palonosetron

					showed values all <10 msec and hence confirmed no effect of palonosetron on cardiac repolarisation in this study. The mean changes observed in Heart Rate, PR and QRS duration, as well as QTc duration using all three correction formulae were not found to be of any clinical significance. No outliers were found for Heart Rate, PR and QRS duration. No late affects were noted to occur. No changes in ECG wave form morphology were identified. In addition, analyses to determine the PK/PD relationship between plasma concentrations of palonosetron after intravenous administration and ECG QT and corrected QT intervals found no statistical or experimental evidence to demonstrate any potential relationship for corrected QT interval or QT intervals and plasma palonosetron concentrations after single dose administration of intravenous palonosetron. The package leafet has been amended in order to completely reflect the existing SPC warning for 5HT3 antagonists to exercise caution when used concomitantly with medicinal products that increase the QT interval or in patients with a personal or family history of QT prolongation.
II/0012	Update of SPC section 4.2 to remove the information that repeated dosing within a 7day interval is not recommended based on clinical study data which will be also summarised in SPC section 5.2. In addition, the ATC code has been added to SPC section 5.1 and the PI is updated in line with the latest QRD template. Minor typographical corrections have been introduced to several languages.	18/12/2008	29/01/2009	SmPC, Labelling and PL	The update section 4.2 was based on 2 clinical studies examining palonosetron administration up to 3 times per week, one study examining 3 daily doses of palonosetron 0.25mg to healthy volunteers and the second study examining alternate daily doses in male patients receiving chemotherapy. Furthermore, a PK simulation (using a two-compartment body model) was performed to produce a plasma concentration time profile for IV palonosetron 0.25 mg given by a 10- second bolus infusion daily for three

	Update of Summary of Product Characteristics, Labelling and Package Leaflet				days. The simulation indicated that AUC(0-INFINITY) for repeated daily dosing of IV palonosetron 0.25 mg over three days was similar to that observed for a single 0.75 mg IV dose, and that the Cmax for each of the three 0.25 mg repeated daily doses was lower than that of a single 0.75 mg dose. With simulation of continued daily dosing of IV palonosetron 0.25 mg to steady state (eight days), the predicted steady state Cmax was lower than the Cmax value after a single 0.75 mg dose based on observed data from study 2092. Therefore it can be concluded that with repeated dosing, accumulation of palonosetron in plasma was predictable based on its long plasma elimination half-life of approximately 40 hours and at steady state Cmax was lower than the Cmax value after a single 0.75 mg dose based on observed data from study 2092. The CHMP considered that the experienced gained form these studies are deemed sufficient to allow removal of the statement from section 4.2 of the SPC. However, to emphasize that Aloxi is not indicated for the prevention or treatment of delayed nausea and vomiting caused by moderate or highly emetogenic therapy further clarifying statements have been added to SPC section 4.2 and 4.4.
IA/0014	IA_05_Change in the name and/or address of a manufacturer of the finished product	29/08/2008	n/a		
N/0011	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	17/07/2008	n/a	Labelling and PL	
IB/0010	IB_10_Minor change in the manufacturing process of	24/01/2008	n/a		

	the active substance				
IB/0009	IB_17_a_Change in re-test period of the active substance	24/01/2008	n/a		
N/0008	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	23/11/2007	n/a	PL	
IA/0007	IA_05_Change in the name and/or address of a manufacturer of the finished product	16/11/2007	n/a		
N/0006	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	13/04/2007	n/a	PL	
N/0005	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	04/04/2006	n/a	PL	
II/0004	Quality changes	26/01/2006	02/02/2006		
IB/0002	IB_33_Minor change in the manufacture of the finished product	22/08/2005	n/a		
N/0003	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	09/08/2005	n/a	Labelling and PL	
N/0001	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	30/05/2005	n/a	PL	