Zinforo

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/0043	Update of section 4.2 of the SmPC in order to provide dosing recommendations for a high-dose regimen of ceftaroline fosamil in paediatric patients for the treatment of complicated skin and soft tissue infections (cSSTI) for which Staphylococcus aureus is known or suspected of having minimum inhibitory concentrations (MIC) of 2 or 4 mg/L based on the final population modelling analysis report (PMAR) of extrapolation study PMAR-EQDD-C266b-DP4-826. In	27/06/2019	25/07/2019	SmPC and PL	For the treatment of complicated skin and soft tissue infections (cSSTI) for which Staphylococcus aureus is known or suspected of having minimum inhibitory concentrations (MIC) of 2 or 4 mg/L, high-dose ceftaroline fosamil regimens of 12 mg/kg to a maximum of 600 mg (120 minutes/every 8 hours) in paediatric patients from 2 years to less than 18 years of age and of 10 mg/kg (120 minutes/every 8 hours) in infants of two months to less than 2 years of age are recommended. High-dose ceftaroline fosamil regimens are

[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).

	addition, the MAH made minor editorial changes to the SmPC. The RMP version 18.1 has also been submitted. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				also recommended for paediatric patients aged from ≥2 years to < 18 years with impaired renal function, in case of creatinine clearance of >30 to ≤ 50 mL/min (10 mg/kg to a maximum of 400 mg) or creatinine clearance of ≥ 15 to ≤ 30 (8 mg/kg to a maximum of 300 mg).
II/0041	Extension of indication to include paediatric patients from birth to less than 2 months old for Zinforo; as a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated based on results from 2 new pharmacokinetic/clinical studies (studies D3720C00006 (P903-21) and D3720C00009 (C2661002)) and a population pharmacokinetic analysis (PMAR-EQDD-C266b-Other-809). The Package Leaflet is updated in accordance. The RMP version 18.1 has also been agreed upon. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	27/06/2019	25/07/2019	SmPC and PL	Please refer to Scientific Discussion of Zinforo-H-C-2252-II-0041.
II/0038	Update of section 4.2 of the SmPC to amend the recommended duration of ceftaroline fosamil intravenous (IV) infusion for standard dose regimens in adults and children. The PL is updated accordingly. In addition the MAH has also taken the opportunity to reformat section 4.2 of the SmPC Posology and method of administration and to incorporate minor editorial updates to sections 4.4, 4.8, 5.1, 5.2 and 5.3 of the SmPC.	29/05/2019	04/07/2019	SmPC and PL	Section 4.2 of the SmPC has been updated to change the recommended duration of ceftaroline fosamil intravenous (IV) infusion for standard dose regimens in adults and paediatrics to a range of 5 to 60 minutes from the currently recommended infusion duration of 1 hour. Data submitted in support of shorter infusion times showed that that reduced infusion times did not affect target attainment (and thus efficacy) and that the safety and tolerability of infusion times as low as 5 minutes is

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				acceptable.
PSUSA/10013 /201810	Periodic Safety Update EU Single assessment - ceftaroline fosamil	16/05/2019	n/a		PRAC Recommendation - maintenance
II/0042	Update of section 4.8 of the SmPC to include revised frequency of the adverse drug reaction (ADR) eosinophilia from not known to rare. The Package leaflet is updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	26/04/2019	04/07/2019	SmPC and PL	Based on the review of data from four phase 3 studies: Studies P903-06 and P903-07 (cSSTI pool) and Studies P903-08 and P903-09 (CAP pool) in which 1305 subjects were treated with ceftaroline fosamil, the frequency of the adverse drug reaction 'eosinophilia' has been revised from 'not known' to 'rare' (1/1305 [0.076%]). Section 4.8 of the SmPC has been updated accordingly.
N/0047	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	09/04/2019	04/07/2019	PL	
IAIN/0046	A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release	01/03/2019	04/07/2019	Annex II and PL	
IA/0045/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 A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder	28/02/2019	n/a		

	or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient 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)				
IA/0039	B.II.d.1.d - Change in the specification parameters and/or limits of the finished product - Deletion of a non-significant specification parameter	26/10/2018	n/a		
N/0040	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	24/10/2018	22/11/2018	PL	
PSUSA/10013 /201710	Periodic Safety Update EU Single assessment - ceftaroline fosamil	17/05/2018	n/a		PRAC Recommendation - maintenance
II/0036	Update of the RMP (version 16) to implement changes from variations EMEA/H/C/002252/II/0029 and EMEA/H/C/002252/II/0022, as requested by PRAC following the latest PSUSA assessment. The update includes the addition of the new population (children from the age of 2 months) as approved in variation II/22; the amendment of the statement concerning additional monitoring following the renewal procedure in which the black triangle symbol was removed from the product information and the re-categorisation of the important identified risks hypersensitivity/anaphylaxis and C. difficile-associated diarrhea as not important. Other minor updates were also included in the revised	08/03/2018	n/a		

	section. The MAH also took the opportunity to revise, reformat and update the content to align with the current RMP template. 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				
IAIN/0035/G	This was an application for a group of variations. A.1 - Administrative change - Change in the name and/or address of the MAH A.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 A.7 - Administrative change - Deletion of manufacturing sites	21/12/2017	22/11/2018	SmPC, Annex II, Labelling and PL	
T/0034	Transfer of Marketing Authorisation	23/06/2017	17/07/2017	SmPC, Labelling and PL	
PSUSA/10013 /201610	Periodic Safety Update EU Single assessment - ceftaroline fosamil	09/06/2017	n/a		PRAC Recommendation - maintenance
R/0031	Renewal of the marketing authorisation.	23/02/2017	24/04/2017	SmPC, Labelling and	Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of Zinforo

				PL	in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.
N/0033	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	24/02/2017	17/07/2017	PL	
II/0029	Update of sections 4.2, 4.4, 5.1 and 5.2 to revise the current posology recommendations for complicated skin and soft tissue infections (cSSTI) produced by resistant S.aureus, to amend the S. aureus clinical breakpoint (Resistant), to update the warning section with additional details on the limitation of the clinical data and to add detail on the levels of creatinine clearance for the different dosages. Consequently the package leaflet is amended. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	26/01/2017	23/02/2017	SmPC and PL	There are limited clinical trial data on the use of ceftaroline to treat cSSTI caused by S. aureus with an minimum inhibitory concentration (MIC) of >1 mg/L. Based on pharmacokinetic and pharmacodynamic analyses the recommended dose regimen for treatment of cSSTI due to S. aureus for which the ceftaroline MIC is 2 or 4 mg/L is 600 mg every 8 hours using 2 hour infusions. Zinforo should not be used to treat cSSTI due to S. aureus for which the ceftaroline MIC is >4 mg/L. Renal impairment for the purposes of dose adjustments was further specified as referring to a creatinine clearance of ≤ 50 mL/min. In section 5.1 of the SmPC, the MIC for resistant to ceftaroline S.aureus has been revised from 1 mg/L to >2 mg/L. For more detailed information please refer to the Summary of Product Characteristics.
IAIN/0030/G	This was an application for a group of variations. C.I.11.a - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of wording agreed by the competent authority C.I.11.a - Introduction of, or change(s) to, the obligations and conditions of a marketing	22/06/2016	n/a		

	authorisation, including the RMP - Implementation of wording agreed by the competent authority C.I.11.a - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of wording agreed by the competent authority C.I.11.a - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of wording agreed by the competent authority C.I.11.a - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of wording agreed by the competent authority C.I.11.a - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of wording agreed by the competent authority				
II/0022	Extension of indication for Zinforo to include a new population, children from the age of 2 months; as a consequence, sections 4.1, 4.2, 4.8, 5.1, 5.2, 5.3 and 6.6 of the SmPC have been updated with new information on dosing, PK and safety. The Package Leaflet is updated in accordance. In addition, the Marketing Authorisation Holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet and to align the PI with the latest QRD template 10.0. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or	28/04/2016	01/06/2016	SmPC, Labelling and PL	Please refer to the scientific discussion for Zinforo EMEA/H/C/002252/II/0022.

	modification of an approved one				
PSUSA/10013 /201510	Periodic Safety Update EU Single assessment - ceftaroline fosamil	13/05/2016	n/a		PRAC Recommendation - maintenance
II/0027	Update of section 4.8 of the SmPC to add agranulocytosis as a rare adverse event. The Package Leaflet is updated accordingly. In addition the MAH took the opportunity to make some minor corrections to the SmPC and Package Leaflet and to update the list of local representatives. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	25/02/2016	01/06/2016	SmPC and PL	
PSUSA/10013 /201504	Periodic Safety Update EU Single assessment - ceftaroline fosamil	19/11/2015	11/01/2016	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10013/201504.
IG/0633	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	09/12/2015	n/a		
II/0024	Update of section 4.4 of the SmPC to add further information on development of a positive direct antiglobulin test (DAGT) following ceftaroline administration every 8 hours. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance	24/09/2015	11/01/2016	SmPC	In this variation the MAH updated the PI with the information that the incidence of DAGT seroconversion in patients receiving ceftaroline fosamil was 10.7% in the four pooled pivotal studies with administration every 12 hours (600 mg administered over 60 minutes every 12 hours) and 32.3% in a study in patients receiving ceftaroline fosamil every 8 hours (600 mg administered over 120 minutes every 8 hours).

	data				
II/0023	Update of the SmPC section 4.8 to add further information on the adverse event 'rash' in Asian patients. In addition, the Marketing authorisation holder (MAH) took the opportunity introduce minor editorial changes to the PI. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	24/09/2015	11/01/2016	SmPC and Annex II	In this variation the MAH updated the PI to add further information on some adverse reactions based on a recently concluded phase III study of 506 adult patients. The most common adverse reactions occurring in ≥3% of patients treated with Zinforo were nausea, headache, and rash. The safety profile of Zinforo was similar to that observed in previous pooled Phase III studies with the exception of a greater incidence of rash in Asian patients.
II/0021	Submission of the final study report of the Multicentre, Randomised, Double-Blind, Comparative Study to Evaluate the Efficacy and Safety of Ceftaroline Fosamil (600 mg every 8 hours) Versus Vancomycin Plus Aztreonam in the Treatment of Patients With Complicated Bacterial Skin and Soft Tissue Infections With Evidence of Systemic Inflammatory Response or Underlying Comorbidities. The RMP v. 14 is updated accordingly. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	24/09/2015	n/a		
PSUSA/10013 /201410	Periodic Safety Update EU Single assessment - ceftaroline fosamil	07/05/2015	n/a		PRAC Recommendation - maintenance
PSUV/0019	Periodic Safety Update	06/11/2014	n/a		PRAC Recommendation - maintenance

II/0016	Submission of a study to update the SmPC and PL with regard to the dosage regime for patients with severe renal impairment. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	25/09/2014	30/10/2014	SmPC, Annex II and PL	Dosage adjustments are required in patients with moderate to severe (CrCL ≥ 15 to ≤ 50 ml/min) renal impairment and End-stage renal disease (ESRD), including patients undergoing haemodialysis: CrCL > 30 to ≤ 50, 400 mg intravenously (over 60 minutes) every 12 hours; CrCL ≥15 to ≤ 30, 300 mg intravenously (over 60 minutes) every 12 hours; ESRD including haemodialysis, 200 mg intravenously (over 60 minutes) every 12 hours. With reference to overdose, ceftaroline can be removed by haemodialysis; over a 4 hour dialysis period, appropximately 74% of a given dose was recovered in the dialysate.
II/0017	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	25/09/2014	30/10/2014	SmPC	
II/0014	Update of section 4.8 of the SmPC in order to add the ADR 'neutropenia' with a frequency 'uncommon'. The Package Leaflet is updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	25/09/2014	30/10/2014	SmPC and PL	The SmPC and PIL for ceftaroline currently list leukopenia as an uncommon adverse reaction within the Blood and lymphatic system disorders SOC. It is therefore considered plausible that this listed effect could also be associated with, or inclusive of, neutropenia. Furthermore, a number of other drugs within the cephalosporin class already list neutropenia in their product information along with leukopenia. The majority of the reports which the MAH presented from its search of the SAPPHIRE database for the ADR neutropenia reported the presence of concomitant medications which were known to be associated with blood dyscrasias such as leukopenia and neutropenia. However, without details of the action taken with these concomitant medications it is difficult to assess the impact these had on causality. There was evidence provided by the MAH from these reports of positive

					de-challenges, including recovery without treatment and reasonable onset times, which is supportive of an association between ceftaroline and neutropenia. The proposal to include neutropenia in the product information was therfore considered acceptable by the CHMP. This alone does not change the benefit-risk balance for the product, which remains positive.
IAIN/0018	A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release	24/07/2014	30/10/2014	Annex II and PL	
IB/0013	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)	08/07/2014	30/10/2014	SmPC	
IAIN/0015/G	This was an application for a group of variations. C.I.11.a - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of wording agreed by the competent authority C.I.11.a - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of wording agreed by the competent authority C.I.11.a - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of wording agreed by the competent authority	03/07/2014	n/a		
II/0011	Submission of the final clinical study report for study	26/06/2014	n/a		The MAH submitted the final report for study D3720C00002,

	D3720C00002 to address a request listed in the RMP. This study was a Phase III, Multicentre, Randomised, Double-Blind, Comparative Study to Evaluate the Efficacy and Safety of Intravenous Ceftaroline Fosamil Versus Intravenous Ceftriaxone in the Treatment of Adult Hospitalised Patients With Community-Acquired Bacterial Pneumonia in Asia. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				a study to investigate the efficacy and safety of Zinforo in Asian patients. The efficacy of Ziniforo in the Asian population is similar to that observed in the Western population. No new efficacy or safety concerns were identified from the assessment of the study results and the variation did not result in any amendments to the Product Information.
IB/0012	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	13/06/2014	n/a		
PSUV/0009	Periodic Safety Update	08/05/2014	n/a		PRAC Recommendation - maintenance
II/0008	of a single-dose PK study of ceftaroline fosamil in children from birth to less than 12 years of age with suspected or confirmed infection (study P903-201/D3720C00006). This variation did not propose any amendments to the product information of Zinforo. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	20/03/2014	n/a		This phase 4, multicentre, open-label, sequential, single-dose, prospective study conducted in 53 subjects enrolled in 5 sequential cohorts of descending age who received treatment and were included in the PK population showed that the doses used achieved ceftaroline exposures in the therapeutic range. Ceftaroline plasma concentrations were >1 mg/L in plasma samples collected 3 to 4 hours after the end of the ceftaroline fosamil infusion in all subjects and in plasma samples collected 5 to 7 hours after the end of infusion in the majority of subjects. The mean ceftaroline concentrations in the plasma samples taken at the end of the infusion were lower in the youngest subjects (preterm and term neonates aged <28 days); in contrast, the mean ceftaroline concentrations in PK samples taken in the last

					collection interval (5 to 7 hours after the end of the ceftaroline fosamil infusion) were higher, suggesting that ceftaroline was cleared more slowly by the youngest subjects. There were no deaths and no subjects discontinued from the study due to an adverse event. The most common TEAEs overall were alanine aminotransferase (ALT) increased, aspartate aminotransferase (AST) increased, blood creatine phosphokinase (CPK) increased, blood lactate dehydrogenase (LDH) increased, prothrombin time prolonged, and hyperbilirubinemia.
IG/0402	C.I.8.a - Introduction of or changes to a summary of Pharmacovigilance system - Changes in QPPV (including contact details) and/or changes in the PSMF location	27/02/2014	n/a		
II/0006	To assess the results of a phase 1, single centre, randomised, double-blind, placebo-controlled parallel group study to assess the safety, tolerability, and pharmacokinetics of ceftaroline after different intravenous dose regimens of ceftaroline fosamil to healthy subjects (study D3720C00010). The RMP was consequently updated to version 8. The requested variation proposed no amendments to the PI. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	21/11/2013	n/a		Study D3720C00010 results showed that ceftaroline exhibited linear and time-independent pharmacokinetics, with no appreciable accumulation after q12h or q8h ceftaroline fosamil multiple-dose administration. Ceftaroline fosamil was well tolerated in healthy male volunteers when administered as a single 600 mg intravenous infusion and as multiple 600 mg intravenous infusions every 12 hours or every 8 hours. No new safety concerns were identified.
II/0005	The MAH provided for assessment the completed clinical study D3720C00005 (A phase 1 single centre,	21/11/2013	n/a		Study D3720C00005 provides new data on Asian population exposure. The pharmacokinetic results from this study in

	open label, two groups study to assess the safety and pharmacokinetics of ceftaroline in healthy Chinese volunteers following single and multiple administration of 600 mg ceftaroline fosamil as 60-minute intravenous infusion every 12 hours and as 120-minute intravenous infusion every 8 hours). The requested variation proposed no amendments to the Product Information. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				healthy Chinese adults are similar to those in healthy Caucasian/ non-Asian adults. With either dosage regimen (1-hour infusion of Ceftaroline every 12 hours or every 8 hours), there was no accumulation (except M-1). The elimination half-life in healthy Caucasian/non-Asian adults is approximately 2.5 hours; and the half-life in healthy Chinese adults is similar. The mean steady-state volume of distribution of ceftaroline in healthy Caucasian/non-Asian adults following a single 600 mg intravenous dose of radiolabelled ceftaroline fosamil is 20.3 l, similar to the volume of extracellular fluid. The steady-state volume of distribution in healthy Chinese adults in this study was similar (range 18.7 – 19.2 l). No new safety concerns for healthy Chinese adults were identified within this study.
II/0004	Update of sections 4.2 and 6.6 of the SmPC in order to reflect the data from the completed clinical study D3720C00015, a 2-part, randomised study to assess local tolerability, safety, and PK of ceftaroline in healthy male and female adult volunteers. The Package Leaflet is updated accordingly. Furthermore, the PI is being brought in line with the latest QRD template version 9. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	21/11/2013	30/10/2014	SmPC, Annex II and PL	Study D3720C00015 was a 2-part, randomised study to assess local tolerability, safety, and PK of ceftaroline in healthy male and female adult volunteers (all recruited subjects were male), conducted at a single centre in the United Kingdom and consisting of two parts: part A (n=24), with a randomised, double-blind, 2-way crossover design, evaluated local tolerability and overall safety when ceftaroline fosamil 600 mg or placebo was diluted in 50 mL or 250 mL and infused into the same vein over 60 min every 12 hours for 72 hours. Part B (n=10), had an open-label, randomised, 2-way crossover design, and intended to evaluate the pharmacokinetics of ceftaroline in either 50 mL and 250 mL infusion volumes or 100 mL and 250 mL infusion volumes, depending on the local tolerability results from Part A. Ceftaroline fosamil was well tolerated and no safety concerns were identified in healthy volunteers when 600 mg were diluted in 50 mL and 250 mL and administered as six

					60-minute infusions. A reduced infusion volume did not result in increased AEs and did not affect the local tolerability of ceftaroline fosamil. The differences in infusion volumes did not have any effects on ceftaroline pharmacokinetics. The time-course and exposures of ceftaroline following a single-dose 60-minute infusion of 600 mg ceftaroline fosamil diluted in the different infusion volumes were similar. The differences in infusion volumes did not have any effects on pharmacokinetics of the metabolite ceftaroline M-1.
IB/0002/G	This was an application for a group of variations. 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.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	23/05/2013	n/a		
IB/0003	B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation	25/03/2013	n/a		
IG/0273	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	08/02/2013	n/a		