Cayston

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
N/0097	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	08/07/2024		PL	
PSUSA/283/202309	Periodic Safety Update EU Single assessment - aztreonam (inhalation use)	16/05/2024	n/a		PRAC Recommendation - maintenance

[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).

IB/0094/G	This was an application for a group of variations. 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.1.f - Replacement or addition of a manufacturing site for part or all of the manufacturing process of the FP - Site where any manufacturing operation(s) take place, except batch release, batch control, and secondary packaging, for sterile medicinal products (including those that are aseptically manufactured) excluding biological/ immunological medicinal products	01/09/2023	n/a		
IA/0095/G	This was an application for a group of variations. B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.a.4.c - Change to in-process tests or limits applied during the manufacture of the AS - Deletion	04/07/2023	n/a		

	of a non-significant in-process test				
IB/0093	C.I.3.z - 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 - Other variation	27/02/2023	16/02/2024	SmPC, Annex II, Labelling and PL	
IA/0092/G	This was an application for a group of variations. B.I.b.2.b - Change in test procedure for AS or starting material/reagent/intermediate - Deletion of a test procedure for the AS or a starting material/reagent/intermediate, if an alternative test procedure is already authorised B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	20/12/2022	n/a		
IA/0090	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	12/10/2022	n/a		
IA/0089/G	This was an application for a group of variations. 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	31/05/2022	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				
IA/0088	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	04/04/2022	n/a		
IA/0087/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.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release) A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release)	16/03/2022	n/a		
IA/0086/G	This was an application for a group of variations. 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	07/02/2022	n/a		

	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 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)				
II/0084	B.II.e.1.b.2 - Change in immediate packaging of the finished product - Change in type/addition of a new container - Sterile medicinal products and biological/immunological medicinal products	11/11/2021	n/a		
IB/0085/G	This was an application for a group of variations. B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation B.I.a.4.c - Change to in-process tests or limits applied during the manufacture of the AS - Deletion of a non-significant in-process test B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	27/10/2021	n/a		
N/0083	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	18/05/2021	16/02/2024	PL	

PSUSA/283/202009	Periodic Safety Update EU Single assessment - aztreonam (inhalation use)	06/05/2021	n/a		PRAC Recommendation - maintenance
N/0081	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	12/06/2020	16/02/2024	Labelling	
IA/0080/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 or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient	20/05/2020	n/a		
IG/1247	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)	08/05/2020	n/a		
IB/0078	B.II.e.6.z - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Other variation	30/04/2019	28/04/2020	SmPC and PL	
IB/0077	B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation	14/03/2019	n/a		

II/0075	Submission of an updated RMP for Cayston in order to comply with Revision 2 of the EU-RMP template, in accordance with the revised guidance in the Guideline on good pharmacovigilance practices (GVP) Module V (EMA/838713/2011; Revision 2). RMP Version 8.0 is approved with this variation 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	14/03/2019	n/a		
IA/0076	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	18/12/2018	n/a		
IA/0074	B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	26/10/2018	n/a		
II/0073	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	18/10/2018	n/a		
T/0072	Transfer of Marketing Authorisation	25/04/2018	24/05/2018	SmPC, Labelling and	

				PL	
PSUSA/283/201709	Periodic Safety Update EU Single assessment - aztreonam (inhalation use)	12/04/2018	n/a		PRAC Recommendation - maintenance
IA/0071/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.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place	27/02/2018	n/a		
IA/0069	B.II.b.5.b - Change to in-process tests or limits applied during the manufacture of the finished product - Addition of a new test(s) and limits	21/12/2017	n/a		
IA/0068	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	20/10/2017	n/a		
IB/0065	B.II.f.1.z - Stability of FP - Change in the shelf-life or storage conditions of the finished product - Other	28/09/2017	n/a		

	variation				
IA/0067/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.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	19/09/2017	n/a		
IA/0066	B.II.e.7.a - Change in supplier of packaging components or devices (when mentioned in the dossier) - Deletion of a supplier	19/09/2017	n/a		
N/0064	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	24/07/2017	24/05/2018	Labelling and PL	
IA/0063	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	04/07/2017	n/a		
IA/0062	B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	14/12/2016	n/a		
IB/0061	B.II.d.2.z - Change in test procedure for the finished product - Other variation	15/07/2016	n/a		

R/0058	Renewal of the marketing authorisation.	01/04/2016	26/05/2016	SmPC, Annex II, Labelling and PL	Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of Cayston in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.
IB/0060	B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	24/05/2016	n/a		
IB/0059	B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	11/01/2016	n/a		
IB/0057/G	This was an application for a group of variations. B.II.f.1.a.1 - Stability of FP - Reduction of the shelf life of the finished product - As packaged for sale B.II.f.1.e - Stability of FP - Change to an approved stability protocol	28/08/2015	26/05/2016	SmPC and PL	
IG/0595	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	04/08/2015	n/a		
IA/0055	A.7 - Administrative change - Deletion of manufacturing sites	23/07/2015	n/a		
IG/0583	A.7 - Administrative change - Deletion of manufacturing sites	23/07/2015	n/a		

IA/0053	A.7 - Administrative change - Deletion of manufacturing sites	01/07/2015	n/a		
IA/0052	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	15/04/2015	n/a		
PSUSA/283/201409	Periodic Safety Update EU Single assessment - aztreonam (inhalation use)	10/04/2015	n/a		PRAC Recommendation - maintenance
IB/0051	B.I.d.1.a.4 - Stability of AS - Change in the re-test period/storage period - Extension or introduction of a re-test period/storage period supported by real time data	20/03/2015	n/a		
IG/0521	A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release	26/02/2015	13/05/2015	Annex II and PL	
IB/0048/G	This was an application for a group of variations. B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.I.b.2.b - Change in test procedure for AS or starting material/reagent/intermediate - Deletion of a test procedure for the AS or a starting material/reagent/intermediate, if an alternative test procedure is already authorised	18/11/2014	n/a		

IB/0046/G	This was an application for a group of variations. B.II.e.4.c - Change in shape or dimensions of the container or closure (immediate packaging) - Sterile medicinal products B.II.e.7.a - Change in supplier of packaging components or devices (when mentioned in the dossier) - Deletion of a supplier B.II.e.7.a - Change in supplier of packaging components or devices (when mentioned in the dossier) - Deletion of a supplier	04/11/2014	13/05/2015	SmPC and PL	
IAIN/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 or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient B.I.a.1.a - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer B.I.a.1.a - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The	01/09/2014	n/a		

	proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer				
IG/0469	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	07/08/2014	n/a		
PSUSA/283/201309	Periodic Safety Update EU Single assessment - aztreonam (inhalation use)	25/04/2014	27/06/2014	SmPC	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/283/201309.
II/0038	Update of sections 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC in order to reflect study results obtained in Open-Label Phase 2 Trial GS-US-205-0162 [to Evaluate the Safety and Efficacy of Aztreonam 75 mg Powder in Pediatric Patients with Cystic Fibrosis (CF) and New Onset Lower Respiratory Tract Culture Positive for Pseudomonas aeruginosa (PA)]. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet and to introduce minor corrections to the PL. Furthermore, the MAH proposed this opportunity to adapt the PI in line with the latest QRD template version 9.1 C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	22/05/2014	13/05/2015	SmPC, Annex II and PL	In a Phase 2 open-label study (GS-US-205-0162), 105 paediatric patients aged 3 months to < 18 years (24 patients aged 3 months to <2 years; 25 patients aged 2 to < 6 years; 56 patients aged 6 to < 18 years) with CF and documented initial/new onset P. aeruginosa infection received Cayston 3 times a day for 28 days. Of the 101 patients, all having a positive cultures for P. aeruginosa within 30 days of study enrolment, of whom 56 (55.4%) were free of P. aeruginosa at baseline who completed a 28-day treatment course 89.1% (n= 90) were free of P. aeruginosa at the end of treatment (Day 28) and 75.2% (n=76) were free of P. aeruginosa 1 month after the end of treatment (Day 56). A total of 79 patients who completed a 28-day treatment course and who did not receive an additional antipseudomonal antibiotic during the treatment period were evaluable 6 months after the end of treatment; of these, 58.2% (n=46) remained free of P. aeruginosa throughout this time period. These data provide some evidence of possible benefit of

					early treatment with a single 28-days course of aztreonam. However, data are too limited for final conclusions, particularly with regards to dose recommendations and post-treatment management. The benefit/risk for Cayston 75 mg in the currently approved indication "the suppressive therapy of chronic pulmonary infections due to Pseudomonas aeruginosa in patients with cystic fibrosis (CF) aged 6 years and older." remains unchanged.
IA/0043	B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place	20/05/2014	n/a		
IB/0042	B.I.d.1.a.4 - Stability of AS - Change in the re-test period/storage period - Extension or introduction of a re-test period/storage period supported by real time data	30/04/2014	n/a		
IG/0422	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	28/03/2014	n/a		
II/0040	Update of section 5.2 of the SmPC, is updated in order to align with data on plasma protein binding described in the Company Core Data Sheet (CCDS). C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	20/03/2014	27/06/2014	SmPC	Aztreonam is moderately bound to plasma proteins. A concentration dependent binding is observed, with larger percentages unbound at low concentrations. Based upon these in vitro data, it is proposed to update the SmPC in line with the CCDS, stating that the protein binding of aztreonam in plasma is approximately 77% at clinically relevant plasma concentrations.

II/0037	To assess the results of study GS-US-205-0160, an Open-Label phase 3 trial, to evaluate the safety of aztreonam 75 mg powder and solvent for nebuliser solution/aztreonam for inhalation solution (AZLI) in children with cystic fibrosis (CF) and chronic Pseudomonas aeruginosa (PA) in the lower airways. The requested variation proposes 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	23/01/2014	n/a		The MAH submitted a paediatric safety study (Study GS-US-205-0160, open-label, single-arm), listed in the agreed Paediatric Investigation Plan (Decision - P/0124/2013). The study was not powered for efficacy. The primary endpoint was the percentage of patients who discontinued study drug due to safety or tolerability reasons by day 168. In total 61 paediatric patients (n=2 aged <2 years, n=7 aged 2 to <6 years, n=52 aged 6 to 12 years) were enrolled. All patients in this study received 3 intermittent 28-day courses of aztreonam lysine (AZLI, Cayston) 75 mg TID (28 days on/28 days off) administered via the PARI Investigational eFlow Nebulizer System. AZLI was administered via best method for each patient using SmartMask Baby, SmartMask Kids, or the standard nebulizer mouthpiece. The MAH submitted the secondary efficacy results of 52 paediatric patients aged 6 to 12 years. No conclusion could be drawn from the efficacy results. However, these are in line with the results previously reported in paediatric (and adult) patients. The safety data from this study are consistent with results from the previous phase 2/3 studies and further support the use of AZLI in children with CF and chronic PA infection over repeated courses of treatment. Cough, pyrexia and hemoptysis were the most common reported AEs similar to already reported in the previous studies. Study-drug induced bronchospasm was reported in 2 paediatric patients. These AEs are already addressed in SmPC sections 4.4 and 4.8. The CHMP is of the opinion that based on the newly submitted safety data, no changes to the SmPC are presently warranted.

					The benefit/risk for Cayston 75 mg remains positive in the currently approved indication.
IA/0036	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)	25/09/2013	n/a		
IG/0290	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	03/04/2013	n/a		
IA/0034	B.II.b.5.b - Change to in-process tests or limits applied during the manufacture of the finished product - Addition of a new tests and limits	14/03/2013	n/a		
IB/0033	B.II.b.3.z - Change in the manufacturing process of the finished product - Other variation	09/01/2013	n/a		
N/0032	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	05/12/2012	27/06/2014	PL	
II/0026	To update sections 4.8 Undesirable effects and 5.2 Pharmacokinetic properties of the SmPC in order to align with the latest Company Core Data Sheet (CCDS). The Package Leaflet was proposed to be updated in accordance. Furthermore, the MAH proposed this opportunity to bring the PI in line with the latest QRD template version 8.1 as well as to amend the description of the device control unit. C.I.4 - Variations related to significant modifications	21/06/2012	23/07/2012	SmPC, Annex II, Labelling and PL	Ongoing signal detection activities have resulted in cumulative reviews of arthralgia, joint swelling and dyspnea; as a consequence, the Cayston Company Core Data Sheet (CCDS) has been updated to Version 3, dated 24 October 2011. In placebo-controlled clinical trials, dyspnoea and arthralgia were adverse events that were reported in fewer patients treated with Cayston relative to placebo (10.2% Cayston vs. 11.3% placebo) and (2.8% Cayston vs. 3.8% placebo) respectively. In contrast, joint swelling was an undesirable effect that was reported in a larger percentage of patients

	of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				treated with Cayston relative to placebo (0.5% Cayston vs. 0% placebo). Dyspnoea is a symptom of pulmonary exacerbation, which can occur in patients with cystic fibrosis (CF) lung disease. Extensive antibiotic therapy use in patients with CF can result in allergic responses with musculoskeletal manifestations, including arthralgia and joint swelling. Based on these frequencies, the MAH proposes the amendments to the section 4.8. In order to be in line with the Company Core Data Sheet (CCDS), the MAH also proposes to modify the Pharmacokinetic Properties of the label. Following assessment of proposed changes, a statement is provided on "metabolism" and more information is added to the existing elimination data.
II/0018	The MAH proposed the update of sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 5.3 of the SmPC in order to include paediatric patients aged 6 years and older, to include long-term, repeated use data and to specifically reflect clinical treatment outcomes. The Package Leaflet was proposed to be updated in accordance. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	21/06/2012	23/07/2012	SmPC and PL	Please refer to the scientific discussion of the Assessment Report Cayston-H-996-II-18-AR.
A20/0024	Pursuant to Article 20 of Regulation (EC) No 726/2004, the European Commission requested on 17 November 2011, the opinion of the CHMP on measures necessary to ensure the quality and the	22/02/2012	25/05/2012		Please refer to the assessment report: EMEA/H/C/996/A-20/0024

	safe use of the above mentioned medicinal product further to the inspection findings at the Ben Venue Laboratories (BVL) manufacturing site located in Bedford, Ohio (USA).				
IG/0172	A.7 - Administrative change - Deletion of manufacturing sites	11/05/2012	n/a		
IA/0030/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.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)	25/04/2012	n/a		
IG/0166	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	13/04/2012	n/a		
IB/0028/G	This was an application for a group of variations. B.I.d.1.a.4 - Stability of AS - Change in the re-test period/storage period - Extension or introduction of a re-test period/storage period supported by real time data	12/04/2012	n/a		

	B.I.d.1.b.3 - Stability of AS - Change in the storage conditions - Change in storage conditions of the AS				
IB/0027	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)	23/03/2012	23/07/2012	SmPC	
IB/0020/G	This was an application for a group of variations. B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation	08/11/2011	n/a		
IG/0114/G	This was an application for a group of variations. C.I.9.d - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the safety database 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	17/10/2011	n/a		
IB/0019/G	This was an application for a group of variations. B.II.b.1.f - Replacement or addition of a manufacturing site for part or all of the manufacturing process of the FP - Site where any manufacturing operation(s) take place, except batch	14/10/2011	n/a		

	release, batch control, and secondary packaging, for sterile medicinal products (including those that are aseptically manufactured) excluding biological/ immunological medicinal products B.II.b.3.z - Change in the manufacturing process of the finished product - Other variation				
R/0015	Renewal of the marketing authorisation.	23/06/2011	05/09/2011	SmPC, Annex II, Labelling and PL	Based on the CHMP review of the available information on the status of the fulfilment of Specific Obligations and having confirmed the positive 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. In addition, the CHMP concludes that all Specific Obligations as laid down in Annex II.C to the Opinion of the last Renewal are fulfilled and therefore recommends that a Marketing Authorisation not "subject to specific obligations" be granted.
IG/0078	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	14/07/2011	n/a		
IB/0017	B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation	07/06/2011	n/a		
IA/0016	A.7 - Administrative change - Deletion of manufacturing sites	19/04/2011	n/a		
IG/0047/G	This was an application for a group of variations.	10/03/2011	n/a		

	C.I.9.d - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the safety database C.I.9.e - Changes to an existing pharmacovigilance system as described in the DDPS - Changes in the major contractual arrangements with other persons or organisations involved in the fulfilment of pharmacovigilance obligations and described in the DD C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system				
IB/0014/G	This was an application for a group of variations. B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate 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 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	14/01/2011	n/a		

	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				
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)	04/01/2011	n/a	SmPC and Annex II	
IB/0012	B.II.b.3.z - Change in the manufacturing process of the finished product - Other variation	17/12/2010	n/a		
IB/0010	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	25/11/2010	n/a	SmPC	
IA/0011	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	24/11/2010	n/a		
R/0006	Renewal of the marketing authorisation.	24/08/2010	26/08/2010	SmPC, Annex II and PL	The CHMP reviewed the available information on the status of the fulfilment of the Specific Obligations by the MAH. The Committee confirmed that the quality, safety and efficacy of this medicinal product continue to be adequately and sufficiently demonstrated, and that its benefit risk balance remains positive. The Committee recommended that the Marketing Authorisation remains 'conditional' until the remaining specific obligations are fulfilled.

IA/0009	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	22/07/2010	n/a		
IA/0008	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	12/07/2010	n/a	Annex II	
IA/0007	To tighten the specification limits of the finished product B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits	12/05/2010	n/a		
IB/0004	B.I.d.1.b.3 - Stability of AS - Change in the storage conditions - Change in storage conditions of the AS	11/03/2010	n/a		
IA/0005	B.IV.1.a.1 - Change of a measuring or administration device - Addition or replacement of a device which is not an integrated part of the primary packaging - Device with CE marking	04/03/2010	04/03/2010	SmPC, Labelling and PL	
II/0003	Quality changes	18/02/2010	03/03/2010		To add a manufacturer, Holopack Verpackungstechnik GmbH, with two contiguous manufacturing sites, for the manufacture of the diluent.
IB/0002	IB_13_b_Change in test proc. for active substance - other changes (replacement/addition)	28/01/2010	n/a		

IB/0001	IB_42_a_01_Change in shelf-life of finished product - as packaged for sale	23/10/2009	n/a	SmPC	