Tygacil

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/0121	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	15/09/2022		SmPC and PL	SmPC new text Section 5.1 Proteus spp., Providencia spp., Morganella morganii and Serratia marcescens were moved to "inherently resistant microorganisms". Klebsiella oxytoca moved from "Commonly susceptible microorganisms" to "Species for which acquired

[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).

					resistance may be a problem". For more information, please refer to the Summary of Product Characteristics.
IB/0120	B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation	10/02/2022	n/a		
N/0119	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	01/10/2021		PL	
IA/0118	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	12/08/2021	n/a		
IA/0117	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	15/06/2021	n/a		
IB/0115	B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation	31/03/2021	n/a		
II/0116	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	18/03/2021	10/05/2021	SmPC and PL	
PSUSA/2954/ 202006	Periodic Safety Update EU Single assessment - tigecycline	11/02/2021	n/a		PRAC Recommendation - maintenance

IA/0113	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	07/09/2020	n/a		
IA/0112/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 B.II.e.7.a - Change in supplier of packaging components or devices (when mentioned in the dossier) - Deletion of a supplier	28/08/2020	n/a		
II/0110	Update of sections 4.4 and 4.8 of the SmPC in order to add a recommendation regarding monitoring of coagulation parameters prior to and during tigecycline treatment based on post-marketing data and to update the frequency of the existing adverse drug reaction hypofibrinogenaemia from 'Not known' to 'Rare'. The Package Leaflet is updated accordingly. In addition, the Marketing Authorisation Holder (MAH) took the opportunity to update the PI in line with the Annex to the European Commission guideline on `Excipients in the labelling and package leaflet of medicinal products for human use' (EMA/CHMP/302620/2017 Rev.1) regarding sodium content and to bring the PI in line with the latest QRD template version 10.1.	14/05/2020	10/05/2021	SmPC, Annex II and PL	The SmPC section 4.4 has been updated as follows: Tigecycline may prolong both prothrombin time (PT) and activated partial thromboplastin time (aPTT). Additionally, hypofibrinogenaemia has been reported with the use of tigecycline. Therefore, blood coagulation parameters such as PT or other suitable anticoagulation test, including blood fibrinogen, should be monitored prior to treatment initiation with tigecycline and regularly while on treatment. Special care is recommended in seriously ill patients and in patients also using anticoagulants (see section 4.5). The PL has been updated accordingly.

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
II/0111	Update of section 4.5 of the SmPC in order to add drug interaction information regarding the concomitant use of tigecycline and calcineurin inhibitors, based on pharmacovigilance data; 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	23/04/2020	10/05/2021	SmPC and PL	Section 4.8 of the SmPC has been updated as follows: Concomitant use of tigecycline and calcineurin inhibitors such as tacrolimus or cyclosporine may lead to an increase in serum trough concentrations of the calcineurin inhibitors. Therefore, serum concentrations of the calcineurin inhibitor should be monitored during treatment with tigecycline to avoid drug toxicity. The Package Leaflet is updated accordingly.
N/0109	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	02/12/2019	10/05/2021	PL	
IA/0107/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.III.1.a.2 - Submission of a new/updated or deletion of Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer B.III.1.a.2 - Submission of a new/updated or deletion of Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer	26/04/2019	n/a		

N/0108	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	09/04/2019	10/05/2021	PL	
IA/0106/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 A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites	28/03/2019	n/a		
N/0105	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	24/10/2018	10/05/2021	PL	
T/0104	Transfer of Marketing Authorisation	11/07/2018	30/07/2018	SmPC, Labelling and PL	
PSUSA/2954/ 201706	Periodic Safety Update EU Single assessment - tigecycline	11/01/2018	n/a		PRAC Recommendation - maintenance
N/0102	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	31/01/2017	16/05/2017	Labelling and PL	
IA/0101	B.III.1.a.2 - Submission of a new/updated or deletion of Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer	25/11/2016	n/a		

IA/0100	A.7 - Administrative change - Deletion of manufacturing sites	28/07/2016	16/05/2017	Annex II and PL	
N/0099	Update of the package leaflet with revised contact details of the local representative for Germany. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	17/06/2016	16/05/2017	PL	
IAIN/0098	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	11/05/2016	16/05/2017	SmPC and PL	
R/0095	Renewal of the marketing authorisation.	17/12/2015	22/02/2016	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 Tygacil continues to be favourable. The CHMP is of the opinion that the renewal can be granted with unlimited validity.
IB/0096	B.II.d.2.f - Change in test procedure for the finished product - To reflect compliance with the Ph. Eur. and remove reference to the outdated internal test method and test method number	15/10/2015	n/a		
IB/0097	B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	13/10/2015	n/a		
II/0094	Update of section 5.1 of the SmPC in order to update the safety information based on new clinical data from the QTc clinical study conducted in healthy volunteers.	25/06/2015	22/02/2016	SmPC and PL	No significant effect of a single intravenous dose of tigecycline 50 mg or 200 mg on QTc interval was detected in a randomized, placebo- and active-controlled four-arm

	In addition, the MAH took the opportunity to make minor editorial changes to the SmPC and minor formatting changes to the PL. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				crossover thorough QTc study of 46 healthy subjects.
N/0093	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	24/06/2015	22/02/2016	PL	
II/0092	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	23/04/2015	28/05/2015	SmPC and PL	This is an extension of indication for the restricted use of Tygacil (tigecycline) in paediatric patients ≥8 years to <18 years of age. The agreed indications for tigecycline in children are the same as those approved for adult patients. This decision was based on data two paediatric PK studies, an ascending single-dose study in subjects 8 to 16 years of age recovering from infections (study 110), and a multiple-dose study in patients 8 to 11 years with cSSTI, cIAI, or community-acquired pneumonia (study 2207) supported by data from children who received tigecycline in the setting of compassionate use, data on the paediatric use reported in the literature and data from a summary of the microbiology data from the Tigecycline Evaluation and Surveillance Trial (TEST) of pathogens isolated from children 8 to <18 years of age.
IB/0091	B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	12/02/2015	n/a		

PSUV/0088	Periodic Safety Update	09/01/2015	n/a		PRAC Recommendation - maintenance
II/0089	Submission of the final PASS Study Report; this also incorporates the response to the assessment by the PRAC re ANX 058.4 - the outcome of the previously submitted progress report to delete the obligation to conduct a PASS, as currently stated in Annex II. The Annex II is updated with deletion of the condition for submission of the PASS. 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	18/12/2014	28/05/2015	Annex II	
IA/0090	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	05/12/2014	n/a		
N/0087	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	19/08/2014	17/11/2014	PL	
IA/0086/G	This was an application for a group of variations. B.III.1.a.2 - Submission of a new/updated or deletion of Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer B.I.b.1.d - Change in the specification parameters	14/07/2014	n/a		

	and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.I.b.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)				
IA/0085	A.7 - Administrative change - Deletion of manufacturing sites	13/06/2014	n/a		
IB/0083	B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation	22/05/2014	n/a		
II/0081/G	This was an application for a group of variations. Update of sections 4.5 and 5.2 of the SmPC in order to update the product information with the revised pharmacokinetic results of paediatric study 2074K4-2207-WW, with new information from an in vitro study showing that tigecycline is substrate of P-glycoprotein and with a corresponding statement describing the potential interactions with P-glycoprotein inhibitors in case of coadministration.	21/11/2013	17/11/2014	SmPC	This group of variations updates section 5.2 of the Tygacil SmPC with amended key pharmacokinetic parameters of paediatric study 2074K4-2207-WW after a review of the data as a consequence of the EMA/H/C/0644/A20/0072 article 20 procedure, concluding that the results of this study needed to be confirmed. Sections 4.5 and 5.2 of the SmPC are also updated with new in vitro information showing that tigecycline is a substrate of P-glycoprotein and that coadministration of P-gp inhibitors (e.g. ketoconazole, cyclosporine) or P-gp inducers (e.g. rifampicin) could affect

	This is a group of two variations which proposed amendments to the Summary of Product Characteristics. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation				the pharmacokinetics of tigecycline.
II/0080	Update of sections 4.4 and 4.8 of the SmPC in order to update the safety information by including the most current pooled safety data in the approved indications obtained from four completed phase 3 and phase 4 studies. The Package Leaflet was updated accordingly. The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	21/11/2013	17/11/2014	SmPC and PL	This SmPC update is based on an update of clinical safety data from completed Phase 3 and 4 clinical trials of studies 316, 315, 400 and 900. Safety data from these studies have been pooled with the 6 Phase III studies from the MAA (10 studies total). The update in section 4.4 of the SmPC for cIAI is based on studies 301,306,315, 316 and 400 and for cSSTI is based on studies 300,305 and 900. As the number of all subjects treated has changed, the proportions of indications and special populations treated with Tygacil have changed. In section 4.8 of the SmPC, the frequency of sepsis/septic shock, hyponatraemia and injection site reaction have upgraded from uncommon to common. In addition, the number of cSSTI and cIAI patients treated with Tigecycline has included the patients of the studies phase III and IV completed during the post-marketing. The number of subjects with nausea or vomiting and the number of subjects with infection-related serious adverse events or sepsis/septic shock has been updated taking into account the Phase III and IV integrated data.
IA/0082	B.II.c.3.z - Change in source of an excipient or reagent with TSE risk - Other variation	22/10/2013	n/a		

IB/0079	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	27/08/2013	15/11/2013	SmPC, Annex II and PL	
N/0078	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	12/07/2013	15/11/2013	Labelling and PL	
IB/0077/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.4.b - Change to in-process tests or limits applied during the manufacture of the AS - Addition of a new in-process test and limits B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a	14/05/2013	n/a		

	non-significant specification parameter (e.g. deletion of an obsolete parameter) 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.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.I.b.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 B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits 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.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.I.b.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 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.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting				

	material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation 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.c.2.c - Change in the specification parameters and/or limits of the immediate packaging of the AS - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) 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 B.I.d.1.z - Stability of AS - Change in the re-test period/storage period or storage conditions - Other variation B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation				
II/0074	Update of Annex II of Tygacil in order to reflect the recent agreed changes in the obligation to conduct post-authorisation measures. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet.	17/01/2013	15/11/2013	Annex II and PL	This variation updates Annex II of Tygacil to reflect the recently agreed changes in the date of submission of the final post-authorisation safety study (PASS) report. The Tygacil Product Information is revised according to the latest QRD template. Local representatives for Cyprus and Greece are

	Furthermore, the PI is being brought in line with the latest QRD template version 8.2. The requested variation proposed amendments to the Annex II and Package Leaflet. 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				updated in the Package Leaflet. Product information affected is: SmPC and Annex II
IA/0076/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 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) 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)	19/12/2012	n/a		

IG/0235/G	This was an application for a group of variations. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation C.I.9.b - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the contact details of the QPPV	06/12/2012	n/a		C.I.z - To replace the Detailed Description of the Pharmacovigilance System (DDPS) with the Pharmacovigilance System Master File (PSMF).
A20/0072	Pursuant to Article 20 of Regulation (EC) No. 726/2004, the European Commission requested the CHMP to re-evaluate the benefit-risk balance of Tygacil in light of newly available data on the deficiencies in conduct of bio-analytical studies performed by the Cetero Research facilities in Houston (Texas, USA) and to give its opinion on whether the marketing authorisation in the approved indication should be maintained, varied, suspended or revoked.	20/09/2012	30/11/2012		Please refer to the assessment report: EMEA/H/C/000644/A-20/0072.
IAIN/0073/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.a - Administrative change - Change in the name and/or address of a manufacturer responsible for batch release A.5.b - Administrative change - Change in the name and/or address of a manufacturer of the finished	12/11/2012	15/11/2013	Annex II and PL	

	product, including quality control sites (excluding manufacturer for batch release) A.7 - Administrative change - Deletion of manufacturing sites				
II/0069	Update of sections 4.4 and 4.8 of the Tygacil SmPC in order to update the safety information to reflect the wording requested by CHMP and additionally warn of the potential development of superinfections (the risk of which is increased in patients with impaired healing of surgical wounds), to add impaired healing as a new adverse drug reaction in section 4.8 and to change the existing stated frequency of thrombocytopaenia in section 4.8 of the SmPC from "not known" to "uncommon" following a cumulative review of the cases identified in the pharmacovigilance and clinical safety database. The PL was updated accordingly. In addition, the MAH took the opportunity to make a minor editorial correction in section 4.8 of the SmPC. Furthermore, the PI is being brought in line with the latest QRD template. 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	19/07/2012	28/08/2012	SmPC, Annex II and PL	This variation updates the Tygacil SmPC safety information to additionally warn of the potential development of superinfections (the risk of which is increased in patients with impaired healing of surgical wounds) and to add impaired healing as a new adverse drug reaction, as requested by CHMP in its adopted conclusions of a follow-up measure in April 2012. The frequency of thrombocytopaenia in section 4.8 of the SmPC is changed from "not known" to "uncommon" following a cumulative review of the cases identified in the pharmacovigilance and clinical safety database.
IB/0070	B.II.c.2.d - Change in test procedure for an excipient - Other changes to a test procedure (including	02/08/2012	n/a		

	replacement or addition)				
IAIN/0071/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 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.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	16/07/2012	n/a		
IG/0169/G	This was an application for a group of variations. C.I.9.e - Changes to an existing pharmacovigilance system as described in the DDPS - Changes in the major contractual arrangements with other persons or organisations involved in the fulfilment of pharmacovigilance obligations and described in the	08/06/2012	n/a		

	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/0067	B.II.b.3.z - Change in the manufacturing process of the finished product - Other variation	08/05/2012	n/a		
IB/0066/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 release, batch control, and secondary packaging, for sterile medicinal products (including those that are aseptically manufactured) excluding biological/ immunological medicinal products 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 currently approved batch size B.II.b.3.z - Change in the manufacturing process of the finished product - Other variation B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation B.II.c.2.a - Change in test procedure for an excipient -	08/05/2012	n/a		

	Minor changes to an approved test procedure				
IA/0065	B.I.c.1.a - Change in immediate packaging of the AS - Qualitative and/or quantitative composition	06/02/2012	n/a		
T/0063	Transfer of Marketing Authorisation	28/10/2011	21/11/2011	SmPC, Labelling and PL	
II/0058	To update section 4.8 of the Tygacil SmPC with additional data from 6 patients with complicated inter-abdominal infection trials who died, but did not have an adverse event with an outcome of death. The MAH also took the opportunity to update the wording on the paediatric patients in section 4.2 of the Tyagcil SmPC to bring it in line with the current SmPC guideline. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	22/09/2011	27/10/2011	SmPC	This type II variation aimed to include 6 patients with complicated intra-abdominal infections, enrolled in the Tygacil phase 3 trials, who died, but whose death was not the outcome of an adverse event (in scientific terms these patients "did not have an adverse event with an outcome of death"), in the existing mortality data summary in section 4.8 of the SmPC. CHMP acknowledged that all previous mortality analyses were based on patients whose death was the outcome of an adverse event (in scientific terms patients which "had an adverse event with an outcome of death")and that these 6 deaths in cIAI patients (2 Tygacil- and 4 comparator treated) from studies 301 and 306 were excluded from these analyses because the events leading to death were not reported in the patient's adverse event case report form. CHMP noted that the current all-cause mortality results presented in section 4.8 of the Tygacil SmPC consist of study-level counts and percent of deaths and agreed that updating the results according to the MAH's proposal would contribute to the mortality data completeness. The MAH also took the opportunity to update the wording on

					the paediatric patients in section 4.2 of the Tygacil SmPC to bring it in line with the current SmPC guideline. Based on the data presented by the MAH, the CHMP agreed to the inclusion of the above updates in sections 4.2. and 4.8 of the Tygacil SmPC. Considering the newly updated mortality data, the CHMP considered that the benefit–risk for Tygacil remains positive.
IB/0059/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.III.1.a.3 - Submission of a new or updated Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - New certificate from a new manufacturer (replacement or addition) B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.c.1.a - Change in immediate packaging of the AS - Qualitative and/or quantitative composition B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS -	21/10/2011	n/a		

	Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS				
IA/0062/G	This was an application for a group of variations. B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.2.b.2 - Change to batch release arrangements and quality control testing of the FP - Including batch control/testing	21/09/2011	n/a	Annex II and PL	
IB/0060	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	19/09/2011	n/a		
II/0057	To update section 5.2 of the SmPC with PK information for Tygacil in the Paediatric population following a request from CHMP of 20 January 2011, which was based on the assessment of the completed paediatric study 3074K4-2207-WW that was originally submitted to the EMA in February 2010, in accordance with Article 46 of Regulation (EC) No1901/2006. C.I.4 - Variations related to significant modifications of	21/07/2011	24/08/2011	SmPC	Additional data from an open label, single, ascending dose study conducted in children aged 8-16 years and aiming to characterize the pharmacokinetics and safety/tolerability of single intravenous doses (0.5 mg/kg, 1 mg/kg and 2 mg/kg) of tigecycline and a phase 2, multicentre, open-label, ascending multiple-dose study to assess the pharmacokinetics, safety and tolerability of tigecycline in paediatric patients from 8 to less than 12 years of age with selected serious infections: complicated intraabdominal infections (cIAI), complicated skin and skin structure

	the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				infections (cSSSI) and community acquired pneumonia(CAP) lead to an update of the Tygacil SmpC with a synopsis of the PK parameters from the two studies and with the information that the safety data observed in the multiple-dose PK study, (although limited due to the small number of children enrolled and to the fact that 3 doses were tested) was consistent with the type of adverse events already reported by adult patients such as nausea, vomiting, pancreatitis etc. Overall, the CHMP agreed that safety and efficacy of tigecycline in children needs to be demonstrated and agreed to include the new paediatric data in the Tygacil SmPC.
IA/0061	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	17/08/2011	n/a		
II/0055	Update of section 4.8 of the SmPC to include Stevens-Johnson syndrome, following a CHMP request after assessment of PSUR 7. In addition, pneumonia and hypoglycaemia have been added as adverse drug reactions to bring the Product Information in line with the Company Core Safety Data Sheet. The PL was updated accordingly C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	19/05/2011	17/06/2011	SmPC and PL	Based on 7 spontaneously reported cases of Stevens Johnson Syndrome, the CHMP agreed to include the adverse events "Severe skin reactions, including Stevens - Johnson syndrome" in section 4.8 of the SmPC. An estimated frequency of Stevens-Johnson syndrome could not be determined for this adverse event since the identified reports include only spontaneous cases and true exposure data from these sources are limited. After a search of the MAH's database, the MAH further identified "Hypoglycaemia" and "Pneumonia" as additional adverse events to be included in section 4.8. Based on an evaluation of the incidences in the pivotal phase III studies the estimated frequencies of pneumonia (1.4%) and hypoglycaemia (1.2%) have been determined to fall within the CIOMS frequency category of Common

WS/0117	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.8.b - Introduction of a new Pharmacovigilance system - which has been assessed by the relevant NCA/EMA for another product of the same MAH	14/04/2011	23/05/2011	Annex II	
R/0053	Renewal of the marketing authorisation.	17/02/2011	06/05/2011	Annex II	
IA/0056	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)	05/05/2011	n/a		
IA/0054	To add an alternative batch size of the active substance (tigecycline). B.I.a.3.a - Change in batch size (including batch size ranges) of AS or intermediate - Up to 10-fold increase compared to the currently approved batch size	24/01/2011	n/a		
IB/0052/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.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation	14/09/2010	n/a		

IB/0048	To add Patheon Italia S.p.A (Viale G.B. Stucchi, 110 20052 Monza (Milano), IT) as a new site for manufacturing, analytical testing and primary packaging. 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	12/08/2010	n/a		
IB/0050	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	05/08/2010	n/a		
II/0033	Update of the Section 6.6 of the Summary of Products Characteristics "Special precautions for disposal and other handling" and Section 6 of the Patient Leaflet "Instructions for use and handling", to include Lactated Ringer's solution for injection as a reconstitution solution and compatible intravenous solution, and to update the information on compatibility for Tygacil diluted in dextrose 50 mg/ml (5 %) solution for injection, when administered through a Y-site. In addition details for local representatives of the	20/05/2010	01/07/2010	SmPC and PL	

	Marketing Authorization Holder for Austria, Germany, Greece, Portugal and Spain have also been updated. Update of Summary of Product Characteristics and Package Leaflet				
IA/0049	B.III.1.a.2 - Submission of a new or updated Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer	24/06/2010	n/a		
IB/0043	B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	22/06/2010	n/a		
IB/0042	B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation	22/06/2010	n/a		
IB/0041	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	22/06/2010	n/a		
IA/0047	B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier	19/05/2010	n/a		
IB/0044	B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of	10/05/2010	n/a		

	specification limits				
IB/0046	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)	06/05/2010	n/a	SmPC	
IB/0045	B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits	05/05/2010	n/a		
II/0034	Update of sections 4.1 and 4.4 of the SmPC based on the results of a clinical study in diabetic foot infections (DFI). Section 1 of the PL has been updated accordingly. Update of Summary of Product Characteristics and Package Leaflet	18/03/2010	29/04/2010	SmPC and PL	The MAH recently completed a phase 3 study comparing tigecycline versus ertapenem for the treatment of diabetic foot infections, which showed that tygecicline did not meet the statistical criteria for non-inferiority to ertapenem at the test-of-cure (TOC) assessment in either of the co-primary efficacy populations. Therefore the MAH submitted this type II variation to update the Summary of Product Characteristics (SPC) and Package Leaflet (PL) to warn physicians and patients that tigecycline is not indicated in the treatment of diabetic foot infection (DFI). As a result section 4.1 and 4.4 of the SmPC and section 1 of the PL have been revised to include updated recommendations.
IA/0040	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	23/04/2010	n/a	Annex II	
IA/0039	C.I.9.g - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the site undertaking pharmacovigilance activities	23/04/2010	n/a	Annex II	

IA/0038	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	23/04/2010	n/a	Annex II	
IA/0037	C.I.9.c - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the back-up procedure of the QPPV	23/04/2010	n/a	Annex II	
IA/0036	C.I.9.a - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the QPPV	23/04/2010	n/a	Annex II	
II/0035	Update of 4.8 of the SmPC, with mortality data from phase 3 and 4 studies in the approved indications cIAI and cSSSI. Update of Summary of Product Characteristics	18/02/2010	26/03/2010	SmPC	Following the review of the last PSUR (15 June 2008 to 14 June 2009), the MAH has submitted this variation to provide updated safety data in severely ill patients and from mortality studies. The analysis was performed using pooled data from a recently completed phase 3 study in DFI and 3 completed phase 4 studies in cIAI and cSSSI. As a result section 4.8 of the SmPC has been revised to include updated information on mortality in the approved indications.
II/0032	Addition of an alternative manufacturer of the finished product. Quality changes	19/11/2009	25/11/2009		
II/0031	Update of the DDPS to reflect a change in the Qualified Person in the EEA for Pharmacovigilance (QPPV). Other administrative and editorial changed have been incorporated in this revised DDPS (version 2.1).	29/05/2009	07/07/2009	Annex II	The MAH submitted a type II variation to update the Detailed Description of the Pharmacovigilance System (DDPS) [Module 1.8.1] to reflect a change in the Qualified Person in the EEA for Pharmacovigilance (QPPV). As part of this

	Changes to QPPV Update of DDPS (Pharmacovigilance)				procedure, data on the deputy QPPV were also included.
II/0030	Update of the Sections 4.4 and 4.8 of the SPC to include precautionary language regarding isolated cases of significant hepatic dysfunction and hepatic failure following the assessment of the PSUR covering the period from 15.12.2007 to 14.06.2008. The section 4 of the PL has been updated accordingly. Additionally the MAH took the opportunity to do some linguistic corrections in all languages with the exception of English and Italian. Update of Summary of Product Characteristics and Package Leaflet	29/05/2009	07/07/2009	SmPC and PL	The CHMP, during this procedure, reviewed all cases of hepatic failure associated with tigecycline. On the basis of this review, the SPC has been updated as follows: - Section 4.8: Hepatic failure has been added as ADR under the frequency category of "not known". - Section 4.4: The wording "Cases of liver injury with a predominantly cholestatic pattern have been reported in patients receiving tigecycline treatment, including some cases of hepatic failure with a fatal outcome. Although hepatic failure may occur in patients treated with tigecycline due to the underlying conditions or concomitant medications, a possible contribution of tigecycline should be considered. (see section 4.8)" has been added in order to reflect isolated cases of significant hepatic dysfunction and hepatic failure which may occur associated to tigecycline treatment.
II/0029	Update of the section 5.1 of the SPC further to the assessment of the PSUR covering the period from 15.12.2007 to 14.06.2008 and the data presented from the Tygecycline Evaluation Surveillance Trial (TEST). Update of Summary of Product Characteristics	29/05/2009	07/07/2009	SmPC	The section 5.1 of the SPC has been updated as follows: - Enterobacter aerogenes, Enterobacter cloacae, Klebsiella pneumoniae and Serratia marcescens have been moved to category 2 of the pathogens table "Species for which acquired resistance may be a problem". - The potential for cross resistance between tigecycline and other antibiotics has been reflected in the SPC.
II/0028	Update of sections 6.2 and 6.6 of the SPC to include information on incompatibility of Tygacil solution with esmoprazole and omeprazole, and compatibility with metoclopramide. The Package Leaflet has been	29/05/2009	07/07/2009	SmPC and PL	The sections 6.2 and 6.6 of the SPC have been updated as follows: - section 6.2: esomeprazole, omeprazole and intravenous solutions that could result in an increase of pH

	updated accordingly. Update of Summary of Product Characteristics and Package Leaflet				above 7 were added to the list of active substances which should not be administered simultaneously through the same Y?site as Tygacil - section 6.6: metoclopramide was added to the list of medicinal products or diluents for which compatibility of Tygacil diluted in sodium chloride 0.9 % for injection, when administered through a Y-site, is demonstrated.
N/0027	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	05/02/2009	n/a	PL	
IA/0026	IA_09_Deletion of manufacturing site	18/11/2008	n/a		
II/0024	Update of section 4.8 of the SPC to include jaundice and liver failure as adverse reactions and section 5.1 to reflect current scientific evidence on resistance of Acinetobacter baumannii. These changes follow assessment of the periodic safety update report covering the period from 15 June 2007 to 14 December 2007. The PL was updated accordingly. Section 4.8 of the SPC was also updated regarding prevalence of acquired resistance to Bacteroides fragilis as agreed in the assessment of the withdrawn variation II.13. Additionally the marketing authorisation holder took the opportunity to update the list of local representatives of the PL and also to correct minor typographical errors in the Slovenian translation. Update of Summary of Product Characteristics and Package Leaflet	25/09/2008	30/10/2008	SmPC and PL	Based on data from clinical trials and the postmarketing setting, a causal relationship for the development of jaundice and liver injury in patients treated with tigecycline cannot be excluded. Therefore the undesirable effects section of the product information was updated to include these adverse events with a frequency of uncommon (the frequency was concluded based on data from clinical trials). Further information regarding susceptibility was available and therefore the product information was updated: decreased susceptibility of the bacteria Acinetobacter baumannii was linked with overexpression of one of the pumps which transports molecules out of the cell (called AdeAB); Bacteroides fragilis bacteria group was moved to the category species for which acquired resistance may be a problem.

IA/0025	IA_15_a_Submission of Ph. Eur. certificate for active substance - approved manufacturer	29/09/2008	n/a		
II/0018	Update of section 4.4 of the SPC to include a precaution reflecting results of the Ventilator Associated Pneumonia subpopulation (VAP) of Study 311. Update of Summary of Product Characteristics	24/04/2008	25/06/2008		
IB/0022	IB_12_a_Change in spec. of active subst./agent used in manuf. of active subst. - tightening	20/05/2008	n/a		
IA/0023	IA_15_a_Submission of Ph. Eur. certificate for active substance - approved manufacturer	19/05/2008	n/a		
IA/0021	IA_08_a_Change in BR/QC testing - repl./add. of batch control/testing site	15/04/2008	n/a		
II/0014	Change in formulation . Sections 6.1, 6.2, 6.4 and 6.6 have been changed. Change in formulation	21/02/2008	27/03/2008	SmPC and PL	The MAH submitted a type II variation to change the approved formulation of Tygacil which contained only the lyophilized active substance. Three additional excipients have been added to the reformulated product, i.e., lactose monohydrate as a diluent and stabiliser, sodium hydroxide and hydrochloric acid for pH adjustment. The formulation was changed in order to provide a more stable medicinal product. As a consequence of the change sections 6.1, 6.2, 6.4 and 6.6 of the SPC have been changed.
II/0012	Update of section 4.8 of the SPC to add information on anaphylactic and anaphylactoid reactions further to	15/11/2007	19/12/2007	SmPC and PL	In the framework of PSUR 3 (covering the period from 15 June 2006 to 14 December 2006), a cumulative review of

	the assessment of PSUR No 3 covering the period from 15 June 2006 to 14 December 2006 following CHMP request. Section 4.4 of the SPC has been updated to include a warning on early detection of the onset or worsening of acute pancreatitis. Section 4.8 of the SPC has been updated to reflect the adverse drug reactions which are listed in section 4.4 of the SPC. Sections 2 and 4 of the PL have been updated accordingly. Update of Summary of Product Characteristics and Package Leaflet				anaphylaxis or anaphylactoid reactions was presented by the Marketing Authorisation Holder (MAH). Based on this review 4 reports of anaphylaxis were identified. In 3 of the 4 reports, the likelihood of a causal association between tigecycline administration and the onset of anaphylaxis could not be excluded. In the fourth report, a temporal and causal association was excluded given the onset of anaphylaxis occurred 9 days following discontinuation of tigecycline administration. Based on this review, the CHMP concluded that the cases of anaphylaxia temporally related to the administration of tigecycline injections strongly suggested a causal relationship and thus section 4.8 of the SPC should be updated to include the adverse reaction anaphylactic reaction. A cumulative review of all study and spontaneous reports of thrombocytopenia coincident with tigecycline use was also performed by the MAH. Overall, since market launch, there have been 27 reports of either thrombocytopenia or platelet count decreased coincident with tigecycline administration. Twenty reports were from spontaneous sources and 7 reports were from a study environment. There were 21 serious reports and 6 non serious reports received. Thus, considering the relevant number of reported cases of thrombocytopenia, most of them serious, the CHMP concluded that a possible causal relationship could not be excluded and that thrombocytopenia should be included in section 4.8 of the SPC. The cumulative information on all spontaneous and study cases of pancreatitis submitted by the MAH included 24 serious and 5 non serious cases (all from studies) of

					pancreatitis. As a result of a general review of the characteristics of the cases, the CHMP concluded that the SPC should be updated to include information on early detection of the onset or worsening acute pancreatitis and the need for specific clini
IA/0020	IA_38_a_Change in test procedure of finished product - minor change to approved test procedure	04/12/2007	n/a		
IB/0019	IB_37_a_Change in the specification of the finished product - tightening of specification limits	29/11/2007	n/a		
II/0015	Update of sections 4.5 and 5.2 of the SPC with information on the action of tigecycline on CYP isoenzymes as requested by the CHMP in March 2007. The MAH took the opportunity to correct minor typographical and formatting errors in Dutch translation. Update of Summary of Product Characteristics	20/09/2007	24/10/2007	SmPC	As committed, at the end of 2006, the MAH submitted a final report of an in vitro study on the investigation of the potential for tigecycline to inhibit CYP450 isoenzymes by mechanism-based inhibition. As requested by the CHMP in March 2007, the MAH submitted this type II variation to modify sections 4.5 "Interaction with other medicinal product and other forms of interaction" and 5.2 "Pharmacokinetic properties" of the SPC to reflect the new findings on inhibition of these CYP enzymes.
IB/0016	IB_10_Minor change in the manufacturing process of the active substance	20/09/2007	n/a		
IA/0017	IA_15_a_Submission of Ph. Eur. certificate for active substance - approved manufacturer	11/09/2007	n/a		
II/0008	Quality changes	19/07/2007	24/07/2007		
II/0006	Update of section 4.4 to amend the statement on pancreatitis to reflect the section 4.8. Update of	24/05/2007	29/06/2007	SmPC, Labelling and	Acute pancreatitis is currently stated as a gastrointestinal disorder in section 4.8 of the SPC with a frequency of

	section 5.1 of the SPC to correct the Minimum Inhibitory Concentration (MIC) breakpoints according to the MIC breakpoints designed by the European Committee on Antimicrobial Susceptibility Testing (EUCAST). In addition typographical errors have been corrected and the QRD template version 7.2 has been implemented to the Product Information. The Package Leaflet (PL) has been updated to include the comments received during a User Readability Testing. The SPC has been updated to include the Marketing Authorisation (MA) date and number. The MA number was also added in the Labelling. Minor editorial corrections have also been included. Update of Summary of Product Characteristics, Labelling and Package Leaflet			PL	reporting of "uncommon". Pancreatitis has been added as a tigecycline specific adverse drug reaction (ADR) in section 4.4 to reflect the information of section 4.8. MIC breakpoints for Streptococcus spp. and Enterococcus spp. have been updated according to the MIC breakpoints defined by EUCAST. Further to the assessment of a follow-up measure, the PL was revised during a User Readability Testing. A real size mock-up of this PL was submitted, which complies with the current font size requirements as stated in the readability guidelines.
IB/0010	IB_10_Minor change in the manufacturing process of the active substance	11/05/2007	n/a		
N/0009	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	20/03/2007	n/a	PL	
IA/0011	IA_15_a_Submission of Ph. Eur. certificate for active substance - approved manufacturer	16/03/2007	n/a		
IA/0007	IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.)	14/02/2007	n/a		
IB/0005	IB_33_Minor change in the manufacture of the finished product	12/01/2007	n/a		

IA/0004	IA_28_Change in any part of primary packaging material not in contact with finished product	29/09/2006	n/a		
IA/0003	IA_13_a_Change in test proc. for active substance - minor change	08/09/2006	n/a		
IA/0002	IA_38_a_Change in test procedure of finished product - minor change to approved test procedure	08/09/2006	n/a		