Zonegran

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
IB/0093	C.I.7.a - Deletion of - a pharmaceutical form	19/02/2019		SmPC, Labelling and PL	
IG/1044/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	22/01/2019	n/a		

[1] Notifications are issued for type I variations and Article 61(3) notifications (unless part of a group including a type II variation or extension application or a worksharing application). Opinions are issued for all other procedures.
[2] A Commission decision (CD) is issued for procedures that affect the terms of the marketing authorisation (e.g. summary of product characteristics, annex II, labelling, package leaflet). The CD is issued within two months of the opinion for variations falling under the scope of Article 23.1a(a) of Regulation (EU) No. 712/2012, or within one year for other procedures.
[3] SmPC (Summary of Product Characteristics), Annex II, Labelling, PL (Package Leaflet).

	B.II.b.2.c.1 - Change to importer, batch release arrangements and quality control testing of the FP - Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing				
IG/1008	B.II.b.2.c.1 - Change to importer, batch release arrangements and quality control testing of the FP - Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing	30/11/2018		Annex II and PL	
PSUSA/3152/ 201803	Periodic Safety Update EU Single assessment - zonisamide	31/10/2018	n/a		PRAC Recommendation - maintenance
T/0090	Transfer of Marketing Authorisation	30/08/2018	21/09/2018	SmPC, Labelling and PL	
IA/0089	A.7 - Administrative change - Deletion of manufacturing sites	30/07/2018	n/a		
IAIN/0088	B.II.b.2.c.1 - Change to importer, batch release arrangements and quality control testing of the FP - Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing	06/07/2018	n/a		
PSUSA/3152/ 201703	Periodic Safety Update EU Single assessment - zonisamide	09/11/2017	08/01/2018	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/3152/201703.

N/0086	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	16/11/2017	21/09/2018	PL	
IA/0084	B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits	22/05/2017	n/a		
IA/0082	B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits	07/04/2017	n/a		
IA/0081	B.I.c.2.a - Change in the specification parameters and/or limits of the immediate packaging of the AS - Tightening of specification limits	07/04/2017	n/a		
IB/0080	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	19/01/2017	08/01/2018	SmPC and PL	
PSUSA/3152/ 201603	Periodic Safety Update EU Single assessment - zonisamide	10/11/2016	04/01/2017	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/3152/201603.
IB/0078	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	24/06/2016	04/01/2017	SmPC, Labelling and PL	
IB/0077	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	25/04/2016	n/a		

PSUSA/3152/ 201503	Periodic Safety Update EU Single assessment - zonisamide	08/10/2015	n/a		PRAC Recommendation - maintenance
IA/0076	A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient	06/07/2015	n/a		
PSUV/0073	Periodic Safety Update	09/10/2014	n/a		PRAC Recommendation - maintenance
IA/0074	B.III.2.b - Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State - Change to comply with an update of the relevant monograph of the Ph. Eur. or national pharmacopoeia of a Member State	19/08/2014	n/a		
II/0072	To add a new active substance manufacturer supported by an ASMF (Active Substance Master File) for the manufacture of hard capsules. B.I.a.1.b - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Introduction of a manufacturer of the AS supported by an ASMF	26/06/2014	n/a		
IB/0071	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	28/05/2014	n/a		

IA/0070	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	11/10/2013	n/a		
II/0065	Extension of Indication for adjunctive treatment of partial seizures with or without secondary generalisation in adult patients to include paediatric patients aged 6 years and above. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	25/07/2013	02/10/2013	SmPC, Annex II and PL	The CHMP variation assessment report will be published as part of the EPAR, following review/deletion of confidential information.
IG/0345	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	03/09/2013	n/a		
IAIN/0068	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	29/04/2013	n/a		
II/0066/G	This was an application for a group of variations. Grouped variation consisting of the following changes: – To add an alternative site for preparation of the capsule blend, encapsulation, and bulk packaging for shipping of Zonegran capsules. – change in the manufacturing process of the finished product. - change to the batch size produced at the alternative manufacturing site	21/02/2013	21/02/2013		

	- addition of an in-process control test to the manufacturing process at the alternative manufacturing site. – change to the container closure system for storage and shipping of the bulk finished product manufactured at the alternative manufacturing site B.II.b.1.e - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non-sterile medicinal products B.II.b.3.b - Change in the manufacturing process of the finished product - Substantial changes to a manufacturing process that may have a significant impact on the quality, safety and efficacy of the medicinal product B.II.b.4.b - Change in the batch size (including batch size ranges) of the finished product - Downscaling down to 10-fold 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 B.II.e.1.z - Change in immediate packaging of the finished product - Other variation				
IB/0067	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	13/02/2013	02/10/2013	SmPC and PL	Update of section 4.8 to include hypersensitivity-type pneumonitis as a result of the final assessment report for PSUR 09. The MAH also updated the contact details of the local representatives for Belgium and Luxembourg.

II/0063	Update of sections 4.8 of the SmPC in order to include alopecia as a “common” adverse reaction as requested by the CHMP consequent to the detection of a possible signal for alopecia associated with Zonegran. The Package Leaflet is updated to amend the changes; “hair loss” has been added as common side effect. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	21/06/2012	20/07/2012	SmPC and PL	The MAH took the opportunity to update the Product Information of Zonegran with the insertion of alopecia as a common adverse reaction. To support the changes a review of the safety data arising from clinical trials, serious/non-serious post-marketing spontaneous reports and reports from literature, has been performed by the MAH.
II/0059	Extension of the approved indication of adjunctive treatment of partial seizures with or without secondary generalisation in adults to include monotherapy in adults with newly diagnosed epilepsy. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	24/05/2012	27/06/2012	SmPC, Annex II and PL	Please refer to the CHMP AR report for this extension variation.
IB/0064/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.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits	15/05/2012	n/a		

II/0060	Update of section 4.8 of the SmPC in order to change in the frequency of pruritus from very rare to common and to add information relating to the increased frequency of certain conditions in the elderly population compared to the adult population, i.e. pruritus and oedema peripheral. Consequentially, the PL is updated as well. Minor editorial changes have been introduced in Annex II. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	16/02/2012	30/03/2012	SmPC, Annex II and PL	The MAH submitted a Type II Variation following a pooled analysis of data in use in the elderly of zonisomide to assess the fulfilment of FUM-005. The pooled data analysis demonstrated that pruritus and oedema peripheral were overall more frequent in the elderly. Data on the adverse event pruritus has also shown that it should be reclassified as a common adverse event rather than a rare adverse event, as previously classified.
IB/0061	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	16/01/2012	30/03/2012	SmPC and PL	Update of section 4.8 of the SmPC to include Drug-Induced Hypersensitivity Syndrome (DIHS) and Drug rash with eosinophilia and systemic symptoms (DRESS) following assessment of PSUR 8. In addition, the local representative section has been updated and minor grammatical corrections have been included in the Latvian and Portuguese Product Information.
IA/0062/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 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) A.7 - Administrative change - Deletion of	19/12/2011	n/a		

	manufacturing sites 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.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits B.III.1.b.2 - Submission of a new or updated Ph. Eur. TSE Certificate of suitability - New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer B.III.1.b.3 - Submission of a new or updated Ph. Eur. TSE Certificate of suitability - Updated certificate from an already approved manufacturer				
IA/0058/G	This was an application for a group of variations. 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 C.I.9.c - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the back-up procedure of the QPPV	06/07/2011	n/a	Annex II	
IB/0057	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	20/06/2011	n/a	SmPC and PL	Following a review of bone disorders associated with the use of Zonegran (FUM 32) the CHMP requested the MAH to update an existing warning in section 4.4 of the SPC to reflect the risk of osteopenia. In addition, the MAH has taken this opportunity to update the local representatives section in the Package Leaflet and to

					introduce minor linguistic corrections.
II/0054/G	This was an application for a group of variations. To delete one significant in-process control(IPC 3) and two non-significant in-process controls (IPC4 and IPC6) in the manufacturing of Zonegran capsules. B.II.b.5.d - Change to in-process tests or limits applied during the manufacture of the finished product - Deletion of an in-process test which may have a significant effect on the overall quality of the finished product B.II.b.5.c - Change to in-process tests or limits applied during the manufacture of the finished product - Deletion of a non-significant in-process test	23/09/2010	29/09/2010		
IB/0056	B.II.b.3.z - Change in the manufacturing process of the finished product - Other variation	24/08/2010	n/a		
IA/0055/G	This was an application for a group of variations. C.I.9.a - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the QPPV C.I.9.b - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the contact details of the QPPV C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system	05/08/2010	n/a	Annex II	

X/0048	Addition of a new pharmaceutical form (orodispersible tablets) in the following strengths 25 mg, 50 mg, 100 mg and 300 mg. Annex I_2.(d) Change or addition of a new pharmaceutical form	20/05/2010	27/07/2010	SmPC, Labelling and PL	
IB/0053	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	16/03/2010	n/a	SmPC and PL	
R/0050	Renewal of the marketing authorisation.	22/10/2009	21/12/2009	SmPC, Annex II, Labelling and PL	Based on the review of the available information, the CHMP is of the opinion that the quality, the safety and the efficacy of this medicinal product continues to be adequately and sufficiently demonstrated and therefore considers the benefit/risk profile of Zonegran continues to be favorable. The CHMP is also of the opinion that the renewal can be granted with unlimited validity. The MAH should continue to submit yearly PSURs.
IB/0052	IA_37_a_Change in the specification of the finished product - tightening of specification limits IB_38_c_Change in test procedure of finished product - other changes	16/11/2009	n/a		
IA/0051	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site IA_08_a_Change in BR/QC testing - repl./add. of	05/08/2009	n/a		

	batch control/testing site IA_07_b_01_Replacement/add. of manufacturing site: Primary packaging site - Solid forms				
II/0044	Update of sections 4.4 and 4.8 of the Summary of Products Characteristics and sections 2 and 4 of the Package Leaflet to include information relating to metabolic acidosis and renal tubular acidosis at the request of the CHMP. In addition, the name of the Portuguese local representative in the Package Leaflet has been updated. Update of Summary of Product Characteristics and Package Leaflet	29/05/2009	07/07/2009	SmPC and PL	Further to the assessment of a Cumulative review of Pharmacovigilance data relating to serious renal adverse events as well as serious hypersensitivity, skin and haematological adverse events (covering the period 1 April 2005 to 30 June 2008) it was concluded that metabolic acidosis is associated with Zonegran treatment. This metabolic acidosis is caused by renal bicarbonate loss due to the inhibitory effect of Zonegran on carbonic anhydrase. The amounts of which bicarbonate is decreased are usually small. The risk of induced metabolic acidosis appears to be more frequent and severe in younger patients. In addition, a signal of renal tubular acidosis was detected in the EudraVigilance database and following the request of CHMP the term was included in the listing of adverse reactions associated with Zonegran.
IB/0049	IA_26_a_Change in the specification of immediate packaging - tightening of specification limits IB_29_b_Change in qual./quant. composition of immediate packaging - all other pharm. forms	11/06/2009	n/a	SmPC	
II/0043	Quality changes	29/05/2009	04/06/2009		
IB/0046	IB_25_a_01_Change to comply with Ph. - compliance with EU Ph. - active substance	26/03/2009	n/a		
IA/0047	IA_01_Change in the name and/or address of the marketing authorisation holder	16/03/2009	n/a	SmPC, Labelling and	

				PL	
IA/0045	IA_08_b_01_Change in BR/QC testing - repl./add. manuf. responsible for BR - not incl. BC/testing	16/02/2009	n/a	Annex II and PL	
II/0041	Update of the section 4.8 of the Summary of Product Characteristics and sections 2 and 4 of the Package Leaflet to include 'toxic epidermal necrolysis' (TEN) under the System Organ Class "Skin and subcutaneous tissue disorders", as a "very rare" adverse effect. Update of Summary of Product Characteristics and Package Leaflet	18/12/2008	11/02/2009	SmPC and PL	Following assessment of a Cumulative Review covering the period 1 April 2005 to 31 March 2008 (submitted with the 5th PSUR), the CHMP requested the MAH to amend the product information (PI) to include the adverse event TEN in the section 4.8 of the Summary of Product Characteristics (SPC). The section has been amended to include TEN. Sections 2 and 4 of the PIL were modified accordingly.
II/0040	Update to the section 4.4 of the Summary of Product Characteristics and the relevant sections of the Package Leaflet following the CHMP assessment of signal of suicidal ideation and behaviour in patients treated with antiepileptics. The MAH took this opportunity to update the Greek and Maltese local representatives in the Package Leaflet. Update of Summary of Product Characteristics and Package Leaflet	18/12/2008	11/02/2009	SmPC and PL	Due to concerns over the potential risk of suicidal thoughts and behaviour in association with the use of antiepileptics, data available from randomized placebo controlled trials and from the post-marketing phase for this class of medicines was considered by the CHMP. Overall, despite the small number of events seen in the clinical trials and the lack of a statistically significant increased risk of suicidal behaviour, the analysis of randomized placebo controlled trials of antiepileptic drugs did not exclude the possibility of an increased risk. Therefore, the CHMP considered it necessary to update section 4.4 of the SPC and section 2 of the PL with information regarding suicidal ideation and behaviour.
IA/0042	IA_25_b_01_Change to comply with Ph. - compliance with EU Ph. update - active substance	08/12/2008	n/a		

IA/0039	IA_37_a_Change in the specification of the finished product - tightening of specification limits	12/09/2008	n/a		
IA/0038	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	17/06/2008	n/a		
II/0031	Update of sections 4.4 and 4.8 of the Summary of Product Characteristics and relevant sections of the Package Leaflet following the assessment of the 4th PSUR. Update of Summary of Product Characteristics and Package Leaflet	21/02/2008	31/03/2008	SmPC and PL	The product information has been amended, at the request of CHMP, to strengthen the warnings on allergic reactions to sulphonamides, and the higher incidence of Stevens-Johnson syndrome (SJS) and Drug Induced Hypersensitivity Syndrome (DIHS) in the elderly. The overall undesirable effects inluded in the SPC and PL have also been reviewed and the following terms have been included: constipation, indigestion, fatigue, flu-like symptoms, slowed thoughts, involuntary movement of the eyes, abnormal skin sensation (pins and needles), tremor, feeling anxious or emotional, blood creatinine increased, ecchymosis (a small bruise caused by blood leaking from broken blood vessels in the skin), status epilepticus (prolonged or repeated seizures) and decreased blood levels of bicarbonate (a substance that prevents blood from becoming acidic). In addition, the undesirable effects frequencies have been amended for insomnia, psychotic disorder (strange or unusual thoughts) and kidney stones.
IA/0037	IA_08_a_Change in BR/QC testing - repl./add. of batch control/testing site	27/03/2008	n/a		
IA/0036	IA_08_a_Change in BR/QC testing - repl./add. of batch control/testing site	27/03/2008	n/a		

IA/0034	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	20/02/2008	n/a		
IA/0033	IA_22_a_Submission of TSE Ph. Eur. certificate for exc. - Approved/new manufacturer	15/02/2008	n/a		
IA/0032	IA_08_b_01_Change in BR/QC testing - repl./add. manuf. responsible for BR - not incl. BC/testing	15/02/2008	n/a	PL	
II/0029	Update of the Package Leaflet following a "User" Test. Update of Package Leaflet	15/11/2007	18/12/2007	PL	The MAH performed a "User" Test to ensure that the Package Leaflet of Zonegran was clear, legible and easy to use. The Package Leaflet has been extensively revised to reflect the recommendation of the test results.
IB/0030	IA_34_a_01_Change in colour/flavour - Reduction or deletion: colouring system IB_34_b_01_Change in colour/flavour - Increase or addition: colouring system	14/12/2007	n/a		
II/0026	Update of section 4.4 of the Summary of Product Characteristics. Update of Summary of Product Characteristics	20/09/2007	29/10/2007	SmPC	Section 4.4 of the Summary of Product Characteristics (SPC) was amended to strengthen warnings on Stevens-Johnson syndrome and rash.
II/0025	Update of section 4.5 of the Summary of Product Characteristics (SPC) and minor changes throughout the labelling and Package Leaflet Update of Summary of Product Characteristics, Labelling and Package Leaflet	20/09/2007	29/10/2007	SmPC, Labelling and PL	Following the submission of interaction studies with zonisamide section 4.5 of the SPC has been updated. In particular, caution is advised when starting or stopping zonisamide treatment or changing the zonisamide dose in patients who are also receiving drugs which are P-gp substrates (e.g. digoxin, quinidine).
N/0027	Minor change in labelling or package leaflet not	11/09/2007	n/a	PL	

	connected with the SPC (Art. 61.3 Notification)				
IA/0028	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	05/09/2007	n/a		
IA/0024	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	30/05/2007	n/a		
IA/0023	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	04/05/2007	n/a		
IB/0022	IB_42_a_01_Change in shelf-life of finished product - as packaged for sale	23/04/2007	n/a		
II/0021	Following the assessment of the second PSUR, the MAH updated the warnings on Stevens-Johnson Syndrome (in section 4.4 of SPC) and on the use of Zonegran during preganancy (in section 4.6 of SPC) and included a reference to aggression, anger and suicidal attempt (in section 4.8 of SPC). The PL was updated accordingly. Update of Summary of Product Characteristics, Labelling and Package Leaflet	22/02/2007	28/03/2007	SmPC, Labelling and PL	The current warning regarding the occurrence of serious rashes in association with Zonegran therapy, including cases of Stevens-Johnson syndrome, has been highlighted in bold and in a box in the product information. The warnings regarding the use of antiepileptic medication during pregnancy and the need of adequate contraception have been tightened and the risk of birth defect in children of women taking anti-epileptic drugs has been highlighted. The product information has also been updated to make reference to anger, aggression and suicide attempt as possible side effects of Zonegran.
IB/0020	IB_41_a_02_Change in pack size - change in no. of units outside range of appr. pack size	12/01/2007	12/01/2007	SmPC, Labelling and PL	

IB/0019	IB_41_a_02_Change in pack size - change in no. of units outside range of appr. pack size	12/01/2007	12/01/2007	SmPC, Labelling and PL	
IA/0018	IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size	24/11/2006	24/11/2006	SmPC, Labelling and PL	
II/0016	Update of section 4.4 of the Summary of Product Characteristics. Update of Summary of Product Characteristics	27/07/2006	07/09/2006	SmPC	Following the evaluation of the first PSUR, the MAH updated the product information to omit the word "isolated" in section 4.4 in relation to the occurrence of agranulocytosis and Stevens Johnson syndrome. Stevens Johnson syndrome and agranulocytosis remain as very rare events.
II/0015	Quality changes	27/07/2006	03/08/2006		
IB/0014	IB_42_a_01_Change in shelf-life of finished product - as packaged for sale	05/04/2006	n/a	SmPC	
N/0013	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	10/02/2006	n/a	PL	
IA/0012	IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.)	11/01/2006	n/a		
IA/0011	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	21/09/2005	n/a		
IA/0010	IA_07_b_01_Replacement/add. of manufacturing site: Primary packaging site - Solid forms	04/08/2005	n/a		
IA/0009	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	10/06/2005	n/a		

IB/0008	IB_41_a_02_Change in pack size - change in no. of units outside range of appr. pack size	26/04/2005	26/04/2005	SmPC, Labelling and PL	
IB/0007	IB_41_a_02_Change in pack size - change in no. of units outside range of appr. pack size	26/04/2005	26/04/2005	SmPC, Labelling and PL	
IB/0006	IB_41_a_02_Change in pack size - change in no. of units outside range of appr. pack size	26/04/2005	26/04/2005	SmPC, Labelling and PL	
IB/0005	IB_41_a_02_Change in pack size - change in no. of units outside range of appr. pack size	26/04/2005	26/04/2005	SmPC, Labelling and PL	
IB/0004	IB_41_a_02_Change in pack size - change in no. of units outside range of appr. pack size	26/04/2005	26/04/2005	SmPC, Labelling and PL	
IA/0003	IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size	18/04/2005	18/04/2005	SmPC, Annex II, Labelling and PL	
IA/0002	IA_22_a_Submission of TSE Ph. Eur. certificate for exc. - Approved/new manufacturer	18/04/2005	n/a		
IA/0001	IA_08_b_01_Change in BR/QC testing - repl./add. manuf. responsible for BR - not incl. BC/testing	18/04/2005	n/a	Annex II and PL	