Keppra

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
WS/2529	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.IV.1.a.3 - Change of a measuring or administration device - Addition or replacement of a device which is	17/10/2024	12/12/2024	SmPC, Labelling and PL	

[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).

	not an integrated part of the primary packaging - Spacer device for metered dose inhalers or other device which may have a significant impact on the delivery of the AS				
WS/2722	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	19/09/2024	12/12/2024	SmPC, Labelling and PL	
IA/0201	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	16/01/2024	n/a		
WS/2339/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Grouped application comprising two type II variations as follows: C.I.4 – Update of section 4.4 of the SmPC in order to add a new warning on lack of efficacy or seizure worsening based on the cumulative review of MAH Global Safety database and published literature. C.I.4 – Update of section 4.8 of the SmPC in order to add a note on obsessive compulsive disorder in the	23/02/2023	06/02/2024	SmPC, Labelling and PL	

	ADR table based on the cumulative review of MAH Global Safety database, clinical studies, data from external spontaneous reporting database and published literature. The Package Leaflet is updated accordingly. In addition, the MAH proposes minor editorial changes of the Labelling. Positive Opinion adopted by consensus. The Icelandic and Norwegian CHMP Members were in agreement with the CHMP recommendation. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
IA/0199/G	This was an application for a group of variations. B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.I.c.1.a - Change in immediate packaging of the AS - Qualitative and/or quantitative composition	21/12/2022	n/a		
PSUSA/1846/ 202111	Periodic Safety Update EU Single assessment - levetiracetam	07/07/2022	n/a		PRAC Recommendation - maintenance

IA/0196/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.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits B.II.d.1.c - Change in the specification parameters and/or limits of the finished product - Addition of a new specification parameter to the specification with its corresponding test method	01/02/2022	n/a		
WS/2067	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Section 4.8 of the SmPC updated to include predisposition of the Japanese population to neuroleptic malignant syndrome (NMS). The package leafleft updated accordingly. In addition, the MAH introduced further editorial changes in the labelling and updated contact details of the MAHs in the package leaflet. The product information was brought in line with the latest QRD template version 10.2. Positive Opinion adopted by consensus. The Icelandic and Norwegian CHMP Members were in agreement with the CHMP recommendation. C.I.4 - Change(s) in the SPC, Labelling or PL due to	02/09/2021	08/07/2022	SmPC, Labelling and PL	

	new quality, preclinical, clinical or pharmacovigilance data				
IA/0195	B.II.e.1.b.3 - Change in immediate packaging of the finished product - Change in type/addition of a new container - Deletion of an immediate packaging container without a complete deletion of a strength or pharmaceutical form	21/07/2021	08/07/2022	SmPC, Labelling and PL	Annexes I, IIIA, IIIB and Annex A have been updated to reflect deletion of presentation EU/1/00/146/030 due to the change in the immediate packaging of the finished product.
WS/1962/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. 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.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 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	11/03/2021	n/a		

IA/0193	B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier	15/02/2021	n/a		
IA/0192	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	13/01/2021	n/a		
WS/1664	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	12/11/2020	17/12/2020	SmPC, Labelling and PL	
WS/1896	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. 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	15/10/2020	17/12/2020	SmPC and PL	
II/0189	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	01/10/2020	n/a		
WS/1827	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.	23/07/2020	17/12/2020	SmPC and PL	

	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				
WS/1751/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.II.b.4.a - Change in the batch size (including batch size ranges) of the finished product - Up to 10-fold compared to the originally approved batch size B.II.b.5.b - Change to in-process tests or limits applied during the manufacture of the finished product - Addition of a new test(s) and limits	26/03/2020	n/a		
IA/0186/G	This was an application for a group of variations. B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place 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	17/01/2020	n/a		
IB/0183/G	This was an application for a group of variations.	16/01/2020	17/12/2020	Annex II and	

	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging 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.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.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 B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process			PL	
PSUSA/1846/ 201811	Periodic Safety Update EU Single assessment - levetiracetam	25/07/2019	04/10/2019	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/1846/201811.
IA/0181	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	05/07/2019	n/a		

IA/0180/G	This was an application for a group of variations. B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	28/06/2019	n/a		
WS/1571	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.II.b.4.z - Change in the batch size (including batch size ranges) of the finished product - Other variation	20/06/2019	n/a		
IAIN/0179	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	06/05/2019	n/a		
IA/0177	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 originally approved batch size	02/04/2019	n/a		
WS/1451	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.4 - Change(s) in the SPC, Labelling or PL due to	28/03/2019	04/10/2019	SmPC and PL	

	new quality, preclinical, clinical or pharmacovigilance data				
IA/0175/G	This was an application for a group of variations. B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place 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 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 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.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	28/02/2019	n/a		

	batch control/testing takes place				
WS/1409	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	08/11/2018	n/a		
II/0169/G	This was an application for a group of variations. Update of section 4.8 of the SmPC to add the ADR Gait Disturbance, to address the CHMP recommendations from P46/085; Update of section 4.2 of the SmPC to add Dysgeusia as a potential experience post administration; Update of Section 4.6 to add information on 'Women of childbearing potential' and to update the Pregnancy section, to address PRAC recommendations from LEG-084.1; The Package Leaflet is updated accordingly. An updated to the Risk Management Plan (version 8.1) is included to address PRAC recommendations from LEG 84.1. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	26/04/2018	28/11/2018	SmPC and PL	The SmPC section 4.2 has been updated as follows: Method of administration The film-coated tablets must be taken orally, swallowed with a sufficient quantity of liquid and may be taken with or without food. After oral administration the bitter taste of levetiracetam may be experienced. The daily dose is administered in two equally divided doses. The SmPC section 4.6 has been updated as follows: Women of child bearing potential Specialist advice should be given to women who are of childbearing potential. Treatment with levetiracetam should be reviewed when a woman is planning to become pregnant. As with all antiepileptic medicines, sudden discontinuation of levetiracetam should be avoided as this may lead to breakthrough seizures that could have serious consequences for the woman and the unborn child. Monotherapy should be preferred whenever possible because therapy with multiple antiepileptic medicines AEDs could be associated with a higher risk of congenital malformations than monotherapy, depending on the associated antiepileptics. Pregnancy

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				A large amount of postmarketing data on pregnant women exposed to levetiracetam monotherapy (more than 1800, among which in more than 1500 exposure occurred during the 1st trimester) do not suggest an increase in the risk for major congenital malformations. Only limited evidence is available on the neurodevelopment of children exposed to Keppra monotherapy in utero. However, current epidemiological studies (on about 100 children) do not suggest an increased risk of neurodevelopmental disorders or delays. Levetiracetam can be used during pregnancy, if after careful assessment it is considered clinically needed. In such case, the lowest effective dose is recommended. Physiological changes during pregnancy may affect levetiracetam concentration. Decrease in levetiracetam plasma concentrations has been observed during pregnancy. This decrease is more pronounced during the third trimester (up to 60% of baseline concentration before pregnancy). Appropriate clinical management of pregnant women treated with levetiracetam should be ensured. Breastfeeding Levetiracetam is excreted in human breast milk. Therefore, breast-feeding is not recommended. However, if levetiracetam treatment is needed during breastfeeding, the benefit/risk of the treatment should be weighed considering the importance of breastfeeding. Fertility No impact on fertility was detected in animal studies (see section 5.3). No clinical data are available, potential risk for human is unknown. The Package Leaflet has been updated accordingly.

IAIN/0171	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	13/04/2018	n/a		
IB/0168	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)	18/12/2017	28/11/2018	SmPC and Labelling	
IB/0170	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	06/12/2017	n/a		
IA/0167	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	12/06/2017	n/a		
N/0166	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	24/03/2017	28/11/2018	Labelling	
IB/0165/G	This was an application for a group of variations. 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.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other	14/03/2017	n/a		

	changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.III.1.a.3 - Submission of a new/updated or deletion of Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - New certificate from a new manufacturer (replacement or addition)				
N/0164	Update of the package leaflet and outer packaging for the oral solution in line with the outcome of the PRAC AR (EMA/PRAC/866401/2016). In addition, the MAH took the opportunity to update the package leaflet with revised contact details of the local representatives for Estonia, Austria, Latvia and Finland. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	12/01/2017	28/11/2018	PL	
II/0162	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	15/12/2016	n/a		
PSUSA/1846/ 201511	Periodic Safety Update EU Single assessment - levetiracetam	15/09/2016	11/11/2016	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/1846/201511
IB/0163	Minor change in the manufacturing process of the active substance levetiracetam (stage 3) to reinstate recrystallization of crude 2-(2-pyrrolidone)-butyramide stage from optional to mandatory. This change only applies to oral solution presentations.	24/10/2016	n/a		

	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS				
IA/0161	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	15/06/2016	n/a		
IA/0160	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	15/06/2016	n/a		
IA/0158	B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation	11/02/2016	n/a		
IA/0156	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	10/12/2015	n/a		
IA/0155	B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits	04/09/2015	n/a		
R/0154	Renewal of the marketing authorisation.	25/06/2015	20/08/2015	SmPC, 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 Keppra continues to be favourable.

					The CHMP is of the opinion that the renewal can be granted with unlimited validity.
IB/0153/G	This was an application for a group of variations. B.III.1.a.3 - Submission of a new/updated or deletion of Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - New certificate from a new manufacturer (replacement or addition) 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	10/12/2014	n/a		
IA/0152/G	This was an application for a group of variations. B.II.e.2.c - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.II.e.2.c - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	25/09/2014	n/a		

	B.II.e.3.b - Change in test procedure for the immediate packaging of the finished product - Other changes to a test procedure (including replacement or addition)				
IB/0151	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	26/06/2014	n/a		
IB/0150/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.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation 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 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 B.II.b.5.b - Change to in-process tests or limits applied during the manufacture of the finished	07/05/2014	n/a		

	product - Addition of a new test(s) and limits 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.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier				
IA/0149/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.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	13/03/2014	n/a		
IB/0148	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	06/03/2014	n/a		
II/0147	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	20/02/2014	n/a		
IB/0146	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	17/01/2014	10/10/2014	SmPC and PL	Based on the cumulative review submitted by the Marketing Authorisation Holder (MAH), the Pharmacovigilance Risk Assessment Committee (PRAC)

					agreed with the MAH to update the Summary of Product Characteristics (SmPC), and the package leaflet according to the wording detailed as follow: • Summary of product characteristics (SmPC): the MAH should update the tabulated list of adverse reactions of the section 4.8 of the SmPC with the PT "hyponatraemia" under the SOC "Metabolism and nutrition disorders", frequency "rare" (≥1/10.000 to < 1/1000). • Package leaflet: the MAH should update the section "4. Possible side effects" with the sentence "decreased blood sodium concentration", frequency "rare". Additionally minor linguistic amendments are implemented to national language versions of France, Finland, Latvia, Poland, Portugal and Sweden.
IA/0145	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	20/12/2013	n/a		
II/0143	Submission of the final report of clinical trial NO1340, comparing the pharmacokinetic properties of Keppra extended release tablets in children and in adults, in line with Article 46 of Regulation (EC) No 1901/2006 (Paediatric Regulation). C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	18/12/2013	n/a		Upon review of study data, the CHMP concluded that the rate and extent to which Keppra extended release tablets was absorbed into the body after repeated oral use was the same for the two age groups compared in the study: children aged 12 to 16 years old and adults aged 18 to 55 years old. No new safety information arose from the study data, but the number of patients included (25) was too small to see if age has an effect on safety. Keppra extended release tablets were not authorised for use in the European Union/European Economic Area at the time of the CHMP opinion.

II/0142	Update of SmPC section 4.8 to include 'drug reaction with eosinophilia and systematic symptoms (DRESS)' as a rare adverse drug reaction. The package leaflet was updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	24/10/2013	10/10/2014	SmPC, Annex II and PL	Following the assessment of Keppra PSUR #15, the company was requested by the Pharmacovigilance Risk Assessment Committee (PRAC) to review all available data for cases of severe hypersensitivity reaction, also referred to as drug reaction with eosinophilia and systematic symptoms (DRESS). This review identified 15 reports of patients receiving levetiracetam who had a severe hypersensitivity reaction considered to be possibly a side effect of this medicine. It also showed that severe hypersensitivity reactions were more frequently reported in patients taking levetiracetam than in the general population. Therefore, the CHMP concluded that, although rare, severe hypersensitivity reaction should be included in the product information in the list of adverse drug reactions.
WS/0411	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	24/10/2013	n/a		
PSUV/0140	Periodic Safety Update	27/06/2013	26/08/2013	SmPC and PL	Please refer to Keppra-H-C-277-PSU-140 EPAR Scientific conclusions and grounds recommending the variation to the terms of the marketing authorisation.
IA/0139/G	This was an application for a group of variations. B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-	13/06/2013	n/a		

	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) 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.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure				
WS/0347/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Addition of 2 manufacturing sites for the intermediates of the active substance levetiracetam. The specifications and the quality control of the intermediates and the active substance have remained unchanged.	25/04/2013	n/a		

	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				
IA/0138/G	This was an application for a group of variations. B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier	09/04/2013	n/a		
IA/0136	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	03/12/2012	n/a		
IG/0222	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	16/11/2012	n/a		
WS/0242/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.	20/09/2012	25/10/2012	SmPC and Labelling	

	Addition of a new presentation with an alternative stopper and an alternative seal for Keppra/Kepcet 100 mg/ml concentrate for solution for infusion (IV). In addition, the MAH took the opportunity to make minor amendments to module 3.2.P.7 (Container Closure System) for Keppra. B.II.e.1.a.3 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Sterile medicinal products and biological/immunological medicinal products B.II.e.6.a - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that affects the product information B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier				
IAIN/0134/G	This was an application for a group of variations. B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within	03/09/2012	29/10/2012	SmPC, Labelling and PL	

	the range of the currently approved pack sizes				
IAIN/0133	B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes	03/09/2012	29/10/2012	SmPC, Labelling and PL	
II/0131	Section 4.8 of the SmPC was updated in order to add 'panic attack' as an undesirable effect following the cumulative review of the safety data for Keppra. The Package Leaflet was updated in accordance. In addition, editorial changes were made to sections 2 and 4.4 of the SmPC and section 2 of the Package Leaflet in order to change the description of the quantity of the sodium excipient in Keppra concentrate for solution for infusion. Moreover, the description of pancytopenia, erythema multiforme, Stevens-Johnsons syndrome and toxic epidermal necrolysis in section 4 of the Package Leaflet was updated. Furthermore, the PI is brought in line with the latest QRD template, version 8. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	19/04/2012	25/05/2012	SmPC, Annex II, Labelling and PL	This variation updated the Keppra Product Information to reflect new safety data arising from a cumulative review of panic attacks based on data from clinical trials and spontaneous reports, which had been requested by the CHMP following the assessment of a previous periodic safety update report. Post-marketing data of this review provided evidence of a possible causal relationship between panic attacks and the use of Keppra and consequently panic attack was included as an uncommon undesirable effect in the Keppra Product Information. Furthermore, the description of the quantity of sodium of Keppra concentrate for solution for infusion was clarified and now reflects the amount of sodium per vial instead of maximum single dose.
WS/0195/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.	15/12/2011	15/12/2011		

	Based on experience at both manufacturing sites, the specification of the film-coated tablets for centrally authorised Keppra and two decentralised products Levetiracetam UCB and Kepcet is proposed to be revised - reduction of the frequency of the water content testing for release analysis - addition of identification test by achiral HPLC for release and shelf-life testing - replacement of the mass uniformity test (Ph.Eur. 2.9.5) by the test of mass variation (Ph.Eur. 2.9.40) for release and shelf-life analysis - suppression of the chiral HPLC for release and shelf-life testing B.II.d.1.c - Change in the specification parameters and/or limits of the finished product - Addition of a new specification parameter to the specification with its corresponding test method B.II.d.1.f - Change in the specification parameters and/or limits of the finished product - Deletion of a specification parameter which may have a significant effect on the overall quality of the finished product B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition) B.II.d.1.d - Change in the specification parameters and/or limits of the finished product - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter				

IA/0130/G	This was an application for a group of variations. B.II.d.1.d - Change in the specification parameters and/or limits of the finished product - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter B.II.d.1.d - Change in the specification parameters and/or limits of the finished product - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter B.II.d.1.d - Change in the specification parameters and/or limits of the finished product - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter B.II.d.1.d - Change in the specification parameters and/or limits of the finished product - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter B.II.d.1.d - Change in the specification parameters and/or limits of the finished product - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter	28/11/2011	n/a		
IA/0127	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	11/11/2011	n/a		
IG/0121	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	03/11/2011	n/a		

	the pharmacovigilance system				
II/0125	This variation updates the section 4.8 of the SmPC in line with the revised SmPC Guideline (September 2009) as requested by the CHMP at the time of the Keppra renewal in 2010. In the section 4.8 the following subsections have been revised: Summary of the safety profile, Tabulated list of adverse reactions and Paediatric population. As a result frequencies of some adverse reactions have been changed. Moreover, two new adverse reactions have been added: lethargy and muscular weakness. The package leaflet was updated accordingly. Furthermore, changes to the labelling to clarify the differentiation of the three oral presentations and minor editorial updates throughout the PI were introduced. 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	24/10/2011	SmPC, Annex II, Labelling and PL	This variation updated the Keppra Product information so that its format and content is in line with the latest guideline on the Summary of Product Characteristics. Additionally, two new side effects: lethargy and muscle weakness were added to the Product information. Furthermore, the information on the patient age ranges for different oral solution presentations has been simplified.
IA/0126	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)	23/09/2011	n/a		
IA/0124	A.5.a - Administrative change - Change in the name and/or address of a manufacturer responsible for batch release	15/07/2011	n/a	Annex II and PL	

II/0123	Update of relevant sections of the SmPC including section 4.2 and 4.4 to indicate that the tablet formulation is not adapted for use in infants and children under the age of 6 years following the CHMP request from February 2011. The Package leaflet has been updated accordingly. In addition, other changes to the Product Information have been introduced: - removal of the text of a precautionary sticker from the labelling of the 300 ml presentation for oral solution as recommended by the CHMP in March 2011; - revision of the Package leaflet for oral solution to improve instructions for use and update pictograms, and simplify the description of different presentations. Furthermore, the local representatives' details have been updated. 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	29/06/2011	SmPC, Labelling and PL	This variation updated the Keppra Product information to inform users that the tablet should not be given to children under the age of 6 years. Moreover, the instructions on how to use correctly the dosing syringe and adaptor provided in the package have been revised. The Marketing Authorisation Holder also took the opportunity to discontinue the use of a sticker previously agreed to inform users that syringes with volume described in millilitres were being put on the market as this information was considered not needed anymore.
II/0120	Update of the SmPC section 4.8 with terms 'choreoathetosis' and 'dyskinesia' based on the assessment of the Paediatric Safety Report (covering period from 01-Dec-2009 to 31-May-2010) and the latest Company Core Data Sheet. The Package leaflet has been updated accordingly. The MAH also deleted the version number of the DDPS from Annex II in line with the procedural announcement of the CHMP in the October 2010	19/05/2011	29/06/2011	SmPC, Annex II and PL	Following the review of the safety data the Product Information for Keppra has been updated to reflect the fact that the treatment with levetiracetam can lead to the difficulty in controlling movements (choreoathetosis) and uncontrollable muscle spasms affecting the head, torso and limbs (dyskinesia).

	Monthly Report. Additionally, minor editorial changes to improve overall accuracy of the Product information have been introduced. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				
IA/0122	B.III.2.a.1 - Change of specification('s) of a former non Pharmacopoeial substance to comply with the Ph. Eur. or with a national pharmacopoeia of a Member State - AS	19/04/2011	n/a		
IA/0121	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	22/03/2011	n/a		
IA/0119	A.7 - Administrative change - Deletion of manufacturing sites	14/02/2011	n/a		
N/0118	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	02/02/2011	n/a	Labelling and PL	
II/0117	Change to the specifications of an intermediate synthesis of the MCC synthesis -intermediate of synthesis produced at step 5b of the MCC route B.I.b.1.e - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a specification parameter which may have a significant	18/11/2010	14/12/2010		

	effect on the overall quality of the AS and/or the FP				
N/0116	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	22/09/2010	n/a	Labelling and PL	
R/0105	Renewal of the marketing authorisation.	24/06/2010	01/09/2010	SmPC, Annex II, Labelling and PL	Based upon the data that have become available since the last renewal of the Marketing Authorisation, the CHMP considers that the benefit-risk balance of Keppra remains positive, but considers that its safety profile is to be closely monitored for the following reasons: Keppra has been authorised for children from 4 years old (approved September 2005) and more recently for children from 1 month to 4 years old (approved September 2009). Due to the recent addition of these sensitive populations to the therapeutic indication, limited safety information is available in these age groups. The CHMP considers that more safety experience needs to be gained in children, and decided that the MAH should continue to submit yearly PSURs and 6-monthly specific safety reports for children < 4 years old in between yearly PSURs. Therefore, based upon the safety profile of Keppra, which requires the submission of yearly PSURs and 6-monthly specific safety reports for children < 4 years old in between yearly PSURs, the CHMP concluded that the MAH should submit one additional renewal application in 5 years time.
IA/0114	B.II.b.2.b.1 - Change to batch release arrangements and quality control testing of the FP - Not including batch control/testing	30/07/2010	n/a	Annex II and PL	
IB/0112	B.II.f.1.b.1 - Stability of FP - Extension of the shelf life of the finished product - As packaged for sale	15/07/2010	n/a	SmPC	

	(supported by real time data)				
IB/0111	B.II.f.1.b.2 - Stability of FP - Extension of the shelf life of the finished product - After first opening (supported by real time data)	15/07/2010	n/a	SmPC, Labelling and PL	
IA/0113	A.7 - Administrative change - Deletion of manufacturing sites	15/07/2010	n/a		
N/0115	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	13/07/2010	n/a	Labelling and PL	
II/0106	Update of the SPC to include the undesirable effects toxic epidermal necrolysis, Stevens-Johnson Syndrome and erythema multiforme in section 4.8 of the SPC as post-marketing events. The relevant section of the PL has been updated accordingly. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	20/05/2010	06/07/2010	SmPC and PL	Thirty cases of severe hypersensitivity skin reactions after exposure to levetiracetam have been identified since the launch of Keppra. In twenty of these, concomitant intake or recent exposure to at least one drug which is known to give this kind of reactions has been noted. In the other cases however, the causality of levetiracetam regarding the event could not be ruled out. Therefore, the SPC (section 4.8) was updated to include Stevens-Johnson syndrome, toxic epidermal necrolysis and erythema multiforme as undesirable events observed during the post marketing phase. The PL has been updated accordingly.
IA/0110	To add an alternative stopper 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	08/06/2010	n/a		

IA/0109/G	This was an application for a group of variations. 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.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	04/06/2010	n/a	Annex II	
IB/0107	B.I.a.4.f - Change to in-process tests or limits applied during the manufacture of the AS - Addition or replacement of an in-process test as a result of a safety or quality issue	01/06/2010	n/a		
IA/0108/G	This was an application for a group of variations. 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.4.c - Change to in-process tests or limits applied during the manufacture of the AS - Deletion	28/05/2010	n/a		

	of a non-significant in-process test				
IA/0103	IA_13_a_Change in test proc. for active substance - minor change	13/01/2010	n/a		
II/0097	Paediatric Art. 8 - Changes to the product information	23/07/2009	02/09/2009	SmPC, Labelling and PL	
IA/0102	IA_32_a_Change in batch size of the finished product - up to 10-fold	09/07/2009	n/a		
II/0101	Update of the residual acetone content in the asymmetric route of synthesis for levetiracetam (the new limit is set at 700 ppm instead of the provisional limit of 500 ppm) Quality changes	29/05/2009	04/06/2009		
II/0099	Update of section 4.4 of the Summary of Product Characteristics and section 2 of the Package Leaflet following assessment of signals of suicidal ideation and behaviour in patients treated with antiepileptics. Update of Summary of Product Characteristics and Package Leaflet	18/12/2008	26/01/2009	SmPC and PL	Due to concerns over the potential risk of suicidal thoughts and behaviour in association with the use of antiepileptics, available data from randomized placebo controlled trials and from the post-marketing phase for this class of medicines was considered by the CHMP. For Keppra, the CHMP also considered the results of two epidemiological studies conducted by the MAH. Overall, the analysis of randomized placebo controlled trials of antiepileptic drugs did not exclude the possibility of an increased risk. In the two epidemiological studies conducted with Keppra, no significant difference in the time to suicide attempt was found between the users of Keppra and that of any other

					antiepileptics during the observation period, and no significant difference in the suicide attempt rates and survival analyses was found between the continuous or intermittent users of Keppra and those taking any other antieplieptics. The product information for Keppra, which already contained warnings about reported cases of suicide, suicide attempt and suicide ideation, has been updated to reflect the outcome of the class review.
IA/0100	IA_13_a_Change in test proc. for active substance - minor change	18/12/2008	n/a		
IA/0098	IA_05_Change in the name and/or address of a manufacturer of the finished product	20/08/2008	n/a		
IB/0096	IB_10_Minor change in the manufacturing process of the active substance	05/08/2008	n/a		
II/0094	Update of section 4.6 "Pregnancy and Lactation" of the Summary of Product Characteristics. Update of Summary of Product Characteristics	26/06/2008	25/07/2008	SmPC	Based on pregnancy and breastfeeding pharmacokinetic results from published studies, the following wording is added to section 4.6 of the SPC to reflect the decreased levetiracetam concentration during pregnancy: "As with other antiepileptic drugs, physiological changes during pregnancy may affect levetiracetam concentration. Decrease in levetiracetam plasma concentrations has been observed during pregnancy. This decrease is more pronounced during the third trimester (up to 60% of baseline concentration before pregnancy). Appropriate clinical management of pregnant women treated with levetiracetam should be ensured."

					In addition, the following information is added regarding breastfeeding: ''However, if levetiracetam treatment is needed during breastfeeding, the benefit/risk of the treatment should be weighed considering the importance of breastfeeding''.
IB/0093	IB_10_Minor change in the manufacturing process of the active substance	05/03/2008	n/a		
IB/0092	IB_10_Minor change in the manufacturing process of the active substance	25/01/2008	n/a		
II/0085	Update of section 5.2 of the Summary of Product Characteristics to reflect the results of an in vitro study investigating the induction potential of levetiracetam on human hepatic microsomal enzymes. In addition, an amendment is made to the wording of the Labelling (outer packaging) for the concentrate for solution for the infusion presentation to better reflect the actual full content of the vial. Update of Summary of Product Characteristics and Labelling	15/11/2007	21/12/2007	SmPC and Labelling	An in vitro induction study in cultured human hepatocytes (NCD1632) was conducted further to observation of enzyme induction in a previous 104-week carcinogenicity study in the mouse. The study assessed the effect of levetiracetam on enzyme induction, and hepatic drug metabolizing enzyme activities in human hepatocytes in particular. Data generated with study NCD1632 have been used to complement the in vivo interaction data in the levetiracetam SPC, which now contains the following text in the subsection "Biotransformation" of Section 5.2: "[…]In vitro, levetiracetam and its primary metabolite have been shown not to inhibit the major human liver cytochrome P450 isoforms (CYP3A4, 2A6, 2C9, 2C19, 2D6, 2E1 and 1A2), glucuronyl transferase (UGT1A1 and UGT1A6) and epoxide hydroxylase activities. In addition, levetiracetam does not affect the in vitro glucuronidation of valproic acid.

					In human hepatocytes in culture, levetiracetam had little or no effect on CYP1A2, SULT1E1 or UGT1A1. Levetiracetam caused mild induction of CYP2B6 and CYP3A4. The in vitro data and in vivo interaction data on oral contraceptives, digoxin and warfarin indicate that no significant enzyme induction is expected in vivo. Therefore, the interaction of Keppra with other substances, or vice versa, is unlikely. "
IA/0091	IA_08_a_Change in BR/QC testing - repl./add. of batch control/testing site	19/12/2007	n/a	Annex II and PL	
IA/0090	IA_38_a_Change in test procedure of finished product - minor change to approved test procedure	18/12/2007	n/a		
II/0088	Quality changes	15/11/2007	23/11/2007		
II/0086	Quality changes	15/11/2007	23/11/2007		
II/0084	Update of the SPC section 4.4 in relation to the risk of suicidal attempts for patients treated with Keppra. In addition, a clarification to dosing adjustment for adult patients with impaired renal function is introduced in SPC section 4.2. The PL is updated accordingly. Update of Summary of Product Characteristics, Labelling and Package Leaflet	20/09/2007	19/10/2007	SmPC, Labelling and PL	The following wording was introduced in section 4.4 of the SPC to minimize the risk of suicidal attempts for patients treated with Keppra: "Suicide, suicide attempt and suicide ideation have been reported in patients treated with levetiracetam. Patients should be advised to immediately report any symptoms of depression and/or suicidal ideation to their prescribing physician."
IB/0087	IB_10_Minor change in the manufacturing process of the active substance	27/09/2007	n/a		

IA/0089	IA_13_a_Change in test proc. for active substance - minor change	19/09/2007	n/a		
T/0083	Transfer of Marketing Authorisation for Keppra from UCB S.A. to UCB Pharma SA Transfer of Marketing Authorisation	03/07/2007	01/08/2007	SmPC, Labelling and PL	
IB/0079	IB_33_Minor change in the manufacture of the finished product	17/04/2007	n/a		
IA/0082	IA_05_Change in the name and/or address of a manufacturer of the finished product	17/04/2007	n/a	Annex II and PL	
IA/0081	IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.)	16/04/2007	n/a		
IA/0080	IA_05_Change in the name and/or address of a manufacturer of the finished product	16/04/2007	n/a	Annex II and PL	
II/0078	Update of or change(s) to the pharmaceutical documentation	22/02/2007	01/03/2007		
II/0071	This application relates to an extension of the indication for Keppra to include adjunctive therapy in the treatment of primary generalised tonic-clonic (PGTC) seizures in adults and adolescents from 12 years of age with idiopathic generalized epilepsy (IGE). Consequential changes were made to sections 4.4, 4.8 and 5.1. The Package Leaflet (PL) was revised accordingly. The PL was also updated to include the Bulgarian and Romanian local	16/11/2006	04/01/2007	SmPC and PL	The CHMP variation Assessment Report will be published as part of the EPAR after deletion of confidential information.

	representatives. Extension of Indication				
IB/0077	IB_14_b_Change in manuf. of active substance without Ph. Eur. certificate - new manufacturer	08/12/2006	n/a		
II/0073	The MAH applied to amend the section 4.8 of the SPC and section 4 of the Package Leaflet further to the CHMP assessment of the 8th Periodic Safety Update Report (PSUR). The MAH also took this opportunity to update the details of the local representatives in the Package Leaflet and to align the product information with the QRD template version 7.1. Update of Summary of Product Characteristics, Labelling and Package Leaflet	21/09/2006	30/10/2006	SmPC, Labelling and PL	Within the 8th PSUR, the MAH provided a cumulative review of cases of hepatobiliary disorders and/or abnormal liver, pancreatitis and increased amylase/lipase, paresthesia and weight loss, over the period from launch to 30th November 2005. As a result of the 8th PSUR assessment, "Hepatitis", "Liver function test abnormal", "Pancreatitis" "Paresthesia" and "Weight loss" have been included into section 4.8 of the SPC as post-marketing experience. The MAH also discussed five cases of aplastic anaemia resulting in the addition of the following to the term pancytopenia in section 4.8 of the SPC: "with bone marrow suppression identified in some of the cases". The Package Leaflet has been amended accordingly. In addition, a few recent cases of hepatic failure in patients treated with Keppra were received and reviewed as part of this variation, including one well documented. This new safety information triggered the update of the SPC to include "hepatic failure" in section 4.8.
IB/0074	IB_10_Minor change in the manufacturing process of the active substance	28/09/2006	n/a		
II/0063	The MAH applied to broaden the therapeutic indication of Keppra to monotherapy in the treatment of partial onset seizures with or without secondary	28/06/2006	07/08/2006	SmPC and PL	The CHMP variation Assessment Report will be published as part of the EPAR after deletion of confidential information.

	generalization in patients from 16 years of age with newly diagnosed epilepsy. Extension of Indication				
II/0070	The Marketing Authorisation Holder applied for the implementation of a change to section 5.3 of the Summary of Product Characteristics recommended by the CHMP further to the assessment of the results of a 2 year mouse carcinogenicity study. Update of Summary of Product Characteristics	28/06/2006	25/07/2006	SmPC	Levetiracetam was administered to four groups of Crl:CD-1(ICR)BR mice, twice daily (in two equal sub-doses six hours apart) by oral gavage (10 mL/kg) for at least 104-weeks. The study demonstrated that administration of levetiracetam for 2-years to mice did not result in a tumourogenic response and that all non-neoplastic changes had been seen earlier in other repeat dose studies in both rats and mice. Based on these findings the safety margin for any carcinogenic potential in the mouse was increased from 3 to 12 over the maximum recommended human dose (MRHD). As a consequence, it can be stated that levetiracetam has no carcinogenic potential to man at the MHRD.
IA/0075	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	25/07/2006	n/a		
IA/0072	IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.)	13/06/2006	n/a		
II/0061	Extension of Indication	23/03/2006	27/04/2006	SmPC and PL	The CHMP variation Assessment Report will be published as part of the EPAR after deletion of confidential information.
IA/0069	IA_28_Change in any part of primary packaging material not in contact with finished product	25/04/2006	n/a		
IB/0065	IB_10_Minor change in the manufacturing process of the active substance	24/04/2006	n/a		

IB/0064	IB_07_c_Replacement/add. of manufacturing site: All other manufacturing operations ex. batch release	21/04/2006	n/a		
IA/0066	IA_38_a_Change in test procedure of finished product - minor change to approved test procedure	03/04/2006	n/a		
X/0046	Annex I_2.(e) Change or addition of a new route of administration X-3-iv_Change or addition of a new pharmaceutical form	26/01/2006	29/03/2006	SmPC, Annex II, Labelling and PL	
II/0058	Change(s) to the manufacturing process for the active substance	23/02/2006	28/02/2006		
IB/0062	IB_14_b_Change in manuf. of active substance without Ph. Eur. certificate - new manufacturer	28/11/2005	n/a		
IB/0059	IB_10_Minor change in the manufacturing process of the active substance	21/10/2005	n/a		
IA/0060	IA_11_a_Change in batch size of active substance or intermediate - up to 10-fold	13/10/2005	n/a		
IB/0055	IB_14_b_Change in manuf. of active substance without Ph. Eur. certificate - new manufacturer	16/09/2005	n/a		
II/0048	Update of or change(s) to the pharmaceutical documentation	27/07/2005	13/09/2005	SmPC, Labelling and PL	
II/0044	This application relates to new data submitted by the	27/07/2005	13/09/2005	SmPC and PL	Please refer to the Scientific discussion: H-277-II-44.

	MAH to extend Keppra's indication to children from 4 years of age as adjunctive therapy in the treatment of partial onset seizures. Extension of Indication				
IA/0057	IA_13_a_Change in test proc. for active substance - minor change	09/09/2005	n/a		
IA/0056	IA_11_a_Change in batch size of active substance or intermediate - up to 10-fold	30/08/2005	n/a		
IB/0053	IB_13_b_Change in test proc. for active substance - other changes (replacement/addition)	17/08/2005	n/a		
II/0050	Quality changes	27/07/2005	08/08/2005		
IB/0052	IB_10_Minor change in the manufacturing process of the active substance	05/08/2005	n/a		
IA/0051	IA_11_a_Change in batch size of active substance or intermediate - up to 10-fold	04/07/2005	n/a		
IB/0049	IB_13_b_Change in test proc. for active substance - other changes (replacement/addition)	03/06/2005	n/a		
II/0047	Change(s) to the test method(s) and/or specifications for the active substance	26/05/2005	01/06/2005		
R/0045	Renewal of the marketing authorisation.	21/04/2005	31/05/2005	SmPC, Annex II, Labelling	

				and PL	
II/0043	This variation relates to an update of section 5.1 (Pharmacodynamic properties) of the Summary of Product Characteristics to include information emerging from newly available data, which improved the understanding of the mechanism of action of Levetiracetam. Update of Summary of Product Characteristics	17/03/2005	27/04/2005	SmPC	A recent series of primary pharmacodynamic studies provided new information on the mechanism of action of levetiracetam. The moderate ability of levetiracetam to reduce N-type Ca2+ currents and to reduce intracellular Ca2+ release, together with the effect against zinc and ß-carbolines reductions in both GABA- and glycine-gated currents contribute to levetiracetam's antiepileptic mechanism of action. Furthermore, levetiracetam's interaction with SV2A provides a significant contribution to its antiepileptic activity. This information justified an update of section 5.1 of the Keppra SPC.
IB/0039	IB_41_a_02_Change in pack size - change in no. of units outside range of appr. pack size	21/12/2004	21/12/2004	SmPC, Labelling and PL	
N/0041	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	16/12/2004	n/a	Labelling	
IA/0042	IA_11_b_Change in batch size of active substance or intermediate - downscaling	06/12/2004	n/a		
IA/0040	IA_05_Change in the name and/or address of a manufacturer of the finished product	26/11/2004	n/a	Annex II and PL	
IB/0038	IB_10_Minor change in the manufacturing process of the active substance	12/08/2004	n/a		
II/0036	Change in formulation	29/07/2004	04/08/2004		
IB/0037	IB_41_a_02_Change in pack size - change in no. of	15/07/2004	15/07/2004	SmPC,	

	units outside range of appr. pack size			Labelling and PL	
II/0031	Update of Summary of Product Characteristics and Package Leaflet	22/04/2004	13/07/2004	SmPC and PL	This variation relates to an update of section 4.4 (Special Warning and special precautions for use) of the Summary of Product Characteristics, to include a mention of new data that became available on conversion to monotheraphy. The local representatives section of the Package Leaflet has been updated.
II/0032	Quality changes	22/04/2004	26/04/2004		
IB/0035	IB_10_Minor change in the manufacturing process of the active substance	23/03/2004	n/a		
IB/0034	IB_12_b_02_Change in spec. of active subst./agent in manuf. of active subst. - test parameter	23/03/2004	n/a		
IA/0033	IA_13_a_Change in test proc. for active substance - minor change	09/03/2004	n/a		
II/0030	Update of Summary of Product Characteristics and Package Leaflet	17/12/2003	05/02/2004	SmPC, Labelling and PL	Following the CPMP conclusions after assessment of the 5th PSUR for Keppra, the Marketing Authorisation Holder submitted a variation to update section 4.9 (Overdose) of the SPC. Additionally, further to QRD recommendations, the tablets product information has been harmonised in line with the oral solution latest approved documents.
IB/0029	IB_10_Minor change in the manufacturing process of the active substance IA_11_a_Change in batch size of active substance or intermediate - up to 10-fold	12/01/2004	n/a		

II/0028	Change(s) to the manufacturing process for the active substance	20/11/2003	16/12/2003		1 Introduction Levetiracetam, the active substance of Keppra film coated tablets, can be synthesised following two routes, namely the "tartaric acid resolution route of synthesis" or the "synthesis route including a chiral Multicolumn Continuous Chromatography (MCC) separation step". This type II variation proposes Aerojet Fine Chemicals, Rancho Cordavo (USA) as alternative manufacturing site for steps 4 to 7 of the synthesis process using MCC. 2 Chemical, pharmaceutical and biological aspects The MCC manufacturing route of levetiracetam consists of 7 steps. The Multicolumn Continuous Chromatographic (MCC) system is used in step 4, to obtain an extract of levetiracetam (S-enantiomer) from etiracetam (racemic mixture). Crude levetiracetam is obtained is step 5 by evaporation of the solvent from the step-4 extract. The substance is recrystallised from acetone and dried in order to give recrystallised levetiracetam in step 6. In step 7, the dried product is milled. Differences to the approved manufacturing steps include alternative settings for step 4 of the MCC system and differences in batch size. Those changes as well as Quality control, batch results and stabiltity are appropriately documented and found acceptable.

I/0027	05_Change in the colouring system of the product (addition, deletion or replacement of colorant(s))	30/07/2003	28/08/2003	SmPC and PL	
II/0026	Quality changes	25/04/2003	02/05/2003		
X/0018	The new presentation consists of a 100 mg/ml levetiracetam oral solution formulation in a 300 ml amber glass bottle (type III, Ph Eur), with a oral syringe. Except for a limited number of points, which can be addresed as part of post -authorisation commitments, the quality of these new presentation is considered to be acceptable when used in accordance with the conditions defined in the SPC. X-3-iv_Change or addition of a new pharmaceutical form	21/11/2002	03/03/2003	SmPC, Annex II, Labelling and PL	
I/0025	Extension of the shelf-life of Keppra 250, 500, 750 and 1000 mg, film-coated tablets from 2 years to 3 years. 20_Extension of shelf-life as foreseen at time of authorisation	17/01/2003	14/02/2003	SmPC	
II/0020	Update of Summary of Product Characteristics	17/10/2002	14/01/2003	SmPC	
I/0024	13_Batch size of active substance	25/10/2002	30/10/2002		
I/0023	12_Minor change of manufacturing process of the active substance	11/10/2002	23/10/2002		

I/0022	11_Change in or addition of manufacturer(s) of active substance	01/10/2002	09/10/2002		
I/0021	11b_Change in supplier of an intermediate compound used in manufacture of the active substance	20/09/2002	24/09/2002		
II/0015	Update of Summary of Product Characteristics and Package Leaflet	25/04/2002	18/07/2002	SmPC and PL	
I/0019	26_Changes to comply with supplements to pharmacopoeias	22/05/2002	27/05/2002		
I/0017	12_Minor change of manufacturing process of the active substance	15/03/2002	18/03/2002		
N/0016	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	05/02/2002	26/03/2002	Labelling	
I/0014	11b_Change in supplier of an intermediate compound used in manufacture of the active substance	21/11/2001	07/01/2002		
II/0013	Change(s) to the manufacturing process for the active substance	21/09/2001	23/10/2001		
II/0001	Update of or change(s) to the pharmaceutical documentation	03/04/2001	03/05/2001		
I/0006	23_Change in storage conditions	02/03/2001	27/04/2001	SmPC, Labelling and	

				PL	
I/0012	25_Change in test procedures of the medicinal product	09/03/2001	09/04/2001		
I/0011	25_Change in test procedures of the medicinal product	09/03/2001	09/04/2001		
I/0010	25_Change in test procedures of the medicinal product	09/03/2001	09/04/2001		
I/0008	24a_Change in test procedure for starting material/intermediate used in manuf. of active substance	22/01/2001	n/a		
I/0007	12_Minor change of manufacturing process of the active substance	22/01/2001	n/a		
I/0005	11b_Change in supplier of an intermediate compound used in manufacture of the active substance	22/01/2001	n/a		
I/0004	12_Minor change of manufacturing process of the active substance	20/12/2000	n/a		
I/0003	24a_Change in test procedure for starting material/intermediate used in manuf. of active substance	20/12/2000	n/a		
I/0002	12_Minor change of manufacturing process of the active substance	20/12/2000	n/a		