Trobalt

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
IAIN/0043	C.I.12 - Inclusion or deletion of black symbol and explanatory statements for medicinal products in the list of medicinal products that are subject to additional monitoring	11/05/2016		SmPC and PL	
PSUSA/2624/ 201509	Periodic Safety Update EU Single assessment - RETIGABINE	14/04/2016	n/a		PRAC Recommendation - maintenance

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

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IB/0041/G	This was an application for a group of variations. C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	18/03/2016	n/a		
R/0036	Renewal of the marketing authorisation.	19/11/2015	14/01/2016	SmPC, Annex II, Labelling and PL	In light of the available quality, safety and efficacy data, the CHMP was of the view that the benefit-risk balance of Trobalt remains favourable in the adjuvant treatment of adult patients with treatment resistant partial onset seizures which cannot be treated with other combinations of medicines. Eye disorders caused by changes in the centre of the retina (maculopathy) were identified as a new side effect of Trobalt and new techniques including fundus photography and ocular coherence tomography are recommended to be used as part of the already recommended regular eye examinations. Patients with maculopathy should be closely monitored and the benefits of continued treatment should be carefully weight against the risks. Overall, the CHMP recommended the renewal of the marketing authorisation, but considered that another renewal in five years' time was needed.
II/0039	Submission of study PRJ2250, a "Survey of Prescriber Understanding of Specific Risks Associated with TROBALT™"; the RMP is revised to reflect the status and results of the study and the associated conclusion on the effectiveness of current risk minimisation measures (final version 14.0). C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission	17/12/2015	n/a		

	of studies to the competent authority				
II/0038	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	22/10/2015	n/a		
II/0037	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	22/10/2015	n/a		
PSUSA/2624/ 201503	Periodic Safety Update EU Single assessment - RETIGABINE	08/10/2015	n/a		PRAC Recommendation - maintenance
PSUSA/2624/ 201409	Periodic Safety Update EU Single assessment - RETIGABINE	10/04/2015	n/a		PRAC Recommendation - maintenance
IB/0034/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites 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)	09/04/2015	14/01/2016	SmPC, Annex II and PL	
IB/0032	B.I.d.1.a.4 - Stability of AS - Change in the re-test period/storage period - Extension or introduction of a re-test period/storage period supported by real time data	09/12/2014	n/a		
II/0028	Submission of the results of nonclinical investigations related to events of discolouration/pigmentation observed with retigabine. Based on the data assessment, an update of section 4.8 of the SmPC has been considered necessary, in order to update	20/11/2014	24/04/2015	SmPC	Adverse event data from clinical trial subjects showed a rate of event of discolouration of the nails, lips, skin and/or mucosa per patient year of exposure of 3.6%. The cumulative incidences of an event at 1 year, 2 years, 3 years, 4 years and 5 years of exposure are approximately

	the safety information on events of discoloration of the nails, lips, skin and/or mucosa in the product information. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				1%, 1.8%, 4.4%, 10.2% and 16.7% respectively. Approximately 30-40% of clinical trial subjects who were being treated with retigabine and underwent a skin and/or ophthalmological examination had findings of discolouration of nails, lips, skin and/or mucosa or non-retinal ocular pigmentation, and approximately 15-30% of clinical trial subjects who were being treated with retigabine and underwent an ophthalmological examination had retinal pigmentation findings.
PSUV/0029	Periodic Safety Update	09/10/2014	n/a		PRAC Recommendation - maintenance
II/0031/G	This was an application for a group of variations. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	25/09/2014	24/04/2015	SmPC	
IA/0030	A.7 - Administrative change - Deletion of manufacturing sites	23/06/2014	n/a		
II/0023	Update of the posology (section 4.2 of the SmPC) to update the dosing recommendations for patients with end-stage renal disease receiving haemodialysis.	20/03/2014	07/05/2014	SmPC	Results from pharmacokinetic simulations were provided to investigate the impact of haemodialysis on retigabine exposure in patients with end-stage renal disease. These

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				results showed that these patients should take three daily doses as usual on the dialysis day. In addition, a single supplemental dose is recommended immediately after haemodialysis. If breakthrough seizures occur towards the end of dialysis then an additional supplemental dose may be considered at the start of subsequent dialysis sessions. This information has been reflected in the posology section of the SmPC.
II/0025	Submission of the final study report for a non-interventional post-authorisation safety study WEUKBRE5744: European survey of Prescriber Understanding of Risks associated with TROBALT. This study is listed as category III (required) pharmacovigilance activity in the Risk Management Plan for TROBALT. An updated Risk Management Plan reflecting the final results of the study has also been submitted. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	25/04/2014	n/a		The MAH has submitted the final study report for a non-interventional post-authorisation safety study WEUKBRE5744: European survey of Prescriber Understanding of Risks associated with TROBALT. This study is listed as category III (required) pharmacovigilance activity in the Risk Management Plan for TROBALT. An updated Risk Management Plan reflecting the final results of the study has also been submitted.
IB/0027/G	This was an application for a group of variations. B.II.e.5.a.2 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change outside the range of the currently approved pack sizes B.II.e.5.b - Change in pack size of the finished product - Deletion of a pack size(s)	15/04/2014	24/04/2015	SmPC, Labelling and PL	
PSUV/0024	Periodic Safety Update	10/04/2014	n/a		PRAC Recommendation - maintenance

II/0021	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		
N/0020	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	14/10/2013	07/05/2014	Labelling and PL	
II/0014	Update of section 4.1 of the SmPC to restrict the indication to adjunctive treatment of drug-resistant partial onset seizures with or without secondary generalisation in patients aged 18 years or older with epilepsy, where other appropriate drug combinations have proved inadequate or have not been tolerated. In addition, warnings of pigment changes (discolouration) of ocular including the retina, lips, skin and nails have been introduced in section 4.4 and 4.8 of the SmPC with recommendations for ophthalmological examinations before and during treatment. The Package Leaflet has been amended accordingly. In addition, the key messages of the physician's guide have been updated in Annex II and as Trobalt was identified in the list of medicines undergoing additional monitoring, the inverted triangle will be included on the product information. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	30/05/2013	01/07/2013	SmPC, Annex II and PL	The CHMP variation assessment report will be published as part of the EPAR, following review/deletion of confidential information.
IB/0018/G	This was an application for a group of variations.	24/05/2013	01/07/2013	SmPC, Labelling and	

	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) B.II.f.1.z - Stability of FP - Change in the shelf-life or storage conditions of the finished product - Other variation			PL	
II/0016	Update of sections 4.5 of the SmPC to include the results of a clinical drug-drug interaction study. The PL was amended accordingly. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	25/04/2013	01/07/2013	SmPC, Labelling and PL	The MAH has performed a drug-drug interaction in vivo study in healthy volunteers to quantify a potential interaction with digoxine. Based on a study conducted in healthy volunteers, therapeutic doses of Trobalt did not have a clinically relevant effect on digoxin Cmax or AUC. Therefore, no dose adjustment of digoxin is needed.
IG/0279	A.1 - Administrative change - Change in the name and/or address of the MAH	18/04/2013	01/07/2013	SmPC, Labelling and PL	
IG/0275	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	15/03/2013	n/a		
II/0015	Update of section 4.2 and 4.9 of the SmPC with information on the effect of haemodialysis in the concentration of retigabine and section 5.2 with PK information in patients with renal impairment and, following results of study RTG115214 in patients with end stage failure dialysis. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	21/02/2013	01/07/2013	SmPC and Annex II	The effect of haemodialysis on retigabine clearance has been evaluated in a study in patients with end stage renal failure receiving dialysis. As a consequence, sections 4.2, 4.9 and 5.2 of the SmPC have been updated. No changes to the dose and administration are considered necessary in these patients.

IB/0013/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation	13/12/2012	n/a		
II/0012	Update of section 4.5 of the SmPC as a result of drug-drug interaction studies with Oral Contraceptives. Update of the Belgium and Luxembourg local representatives in the Package Leaflet; linguistic amendments to the Italian, Slovenian and French Package leaflet and SmPC were also done. Annex II was updated based on CHMP Assessment of the PSUR 001 and RMP (v.005). C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	19/07/2012	10/09/2012	SmPC, Annex II and PL	Based on the review of the pharmacokinetics data, the wording “At retigabine doses of up to 750 mg/day, there was no clinically significant effect of retigabine on the pharmacokinetics of the estrogen (ethinyl estradiol) or progestogen (norethindrone) components of the oral contraceptive pill. In addition, there was no clinically significant effect of the low dose combination oral contraceptive pill on the pharmacokinetics of retigabine” was added in the section 4.5 of the SmPC.
IG/0150/G	This was an application for a group of variations. C.I.9.c - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the back-up procedure 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	05/04/2012	n/a		

IAIN/0010/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites B.II.b.2.b.1 - Change to batch release arrangements and quality control testing of the FP - Not including batch control/testing	04/04/2012	10/05/2012	Annex II and PL	
II/0003/G	This was an application for a group of variations. Addition of a new synthetic route for the active substance. The approved process remains authorised. B.I.a.1.c - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer uses a substantially different route of synthesis or manufacturing conditions B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.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	17/11/2011	17/11/2011		

	material/intermediate B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.I.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				
IB/0009/G	This was an application for a group of variations. 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.a - Change in the manufacturing process of the finished product - Minor change in the manufacturing process of an immediate release solid oral dosage form or oral solutions B.II.b.4.b - Change in the batch size (including batch size ranges) of the finished product - Downscaling down to 10-fold 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) B.II.b.3.z - Change in the manufacturing process of the finished product - Other variation	15/11/2011	n/a		
IB/0008/G	This was an application for a group of variations. B.II.a.3.a.1 - Changes in the composition (excipients) of the finished product - Changes in components of the flavouring or colouring system - Addition , deletion or replacement B.II.e.1.a.1 - Change in immediate packaging of the finished product - Qualitative and quantitative	27/10/2011	10/05/2012	SmPC and PL	

	composition - Solid pharmaceutical forms				
IB/0007	B.II.b.1.z - Replacement or addition of a manufacturing site for the FP - Other variation	11/08/2011	n/a		
IA/0001/G	This was an application for a group of variations. B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site	26/05/2011	n/a		
IA/0005	B.I.c.3.b - Change in test procedure for the immediate packaging of the AS - Other changes to a test procedure (including replacement or addition)	25/05/2011	n/a		
IA/0004	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	25/05/2011	n/a		
IA/0006	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	23/05/2011	n/a		