Comtess

Procedural steps taken and scientific information after the authorisation

Application number	Scope	Opinion/ Notification[1] issued on	Commission Decision Issued[2] / amended on	Product Information affected[3]	Summary
N/0064	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	05/09/2024		PL	
PSUSA/1223/ 202201	Periodic Safety Update EU Single assessment - entacapone	01/09/2022	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).

WS/2202/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.z - Quality change - Active substance - Other variation B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation	31/03/2022	n/a		
WS/2096	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	21/10/2021	19/05/2022	SmPC, Labelling and PL	
IG/1277	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	08/10/2020	19/05/2022	Annex II and PL	

WS/1735/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.d.1.b.3 - Stability of AS - Change in the storage conditions - Change in storage conditions of the AS B.I.a.2.e - Changes in the manufacturing process of the AS - Minor change to the restricted part of an ASMF	12/03/2020	n/a		
PSUSA/1223/ 201901	Periodic Safety Update EU Single assessment - entacapone	05/09/2019	n/a		PRAC Recommendation - maintenance
N/0058	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	31/07/2019	19/05/2022	PL	
IG/0982/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.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	26/10/2018	n/a		

	the AS -replacement or addition of a site where batch control/testing takes place				
IG/0888	A.7 - Administrative change - Deletion of manufacturing sites	29/01/2018	n/a		
WS/1064	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	15/12/2016	08/01/2018	SmPC, Annex II, Labelling and PL	
PSUSA/1223/ 201601	Periodic Safety Update EU Single assessment - entacapone	02/09/2016	n/a		PRAC Recommendation - maintenance
N/0052	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	18/01/2016	08/01/2018	PL	
N/0051	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	03/06/2015	28/01/2016	PL	
IG/0546	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	27/04/2015	n/a		
WS/0665	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. To update the Product Information as follows:	22/01/2015		SmPC, Labelling and PL	

	- to include ADR statement - to update the PI to QRD template version 9 - to include an explanation to the PL of the pictogram which is currently only displayed on the carton (all products except Comtan) - to correct the local contact information for Malta in Stalevo PL - to correct the local contact information for Latvia in all PLs except for Comtan and Entacapone Orion - to correct the local contact information for Germany in Comtess and Levodopa/Carbidopa/Entacapone Orion - for Comtan only: to add 'Magnesium stearate' to the list of excipients for the film-coating in the SmPC and PL. Tablet core and Film-coating both contain magnesium stearate - to correct linguistic amendments in Annexes - to amend a mistake in the Annex A (only for Comtan). C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation				
N/0048	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	03/07/2014	28/01/2016	PL	
IG/0433/G	This was an application for a group of variations. B.II.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site B.II.b.1.a - Replacement or addition of a	08/05/2014	n/a		

	manufacturing site for the FP - Secondary packaging site				
N/0046	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	14/08/2013	28/01/2016	PL	
WS/0331	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of SmPC sections 4.4 and 4.8 in order to update the safety information by implementing class labelling for the risk of impulse control disorders. C.I.3.z - 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 - Other variation	13/12/2012	24/01/2013	SmPC, Annex II, Labelling and PL	Based on a recent review of the available post-marketing data in relation to the risk of development of impulse control disorders when using medicinal products containing levodopa, dopamine agonists and/or catechol-O-methyltransferase (COMT) inhibitors, the CHMP/PhVWP requested a class labelling to update and harmonise the product information of all products concerned. In response to this request, the product information was updated to reflect behavioural symptoms related to impulse control disorders including compulsive spending or buying, binge eating and compulsive eating. It was clarified that this adverse reaction can occur irrespective of the indication and at normal doses. Furthermore, regular monitoring of patients and a careful review of treatment, if symptoms occur, is recommended. The Package Leaflet was updated in accordance and advice for the patient’s family and carers was provided.
WS/0199	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. 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	19/01/2012	19/01/2012		

II/0043/G	This was an application for a group of variations. The MAH submitted a group of variations to update the SPC sections 4.4 and 4.8 and the PL of Comtess with respect to ischemic heart disease events and myocardial infarction. The SPC section 4.4 and the PL were updated further to the signal on colitis. In addition, the PL has been revised following the results of a user test and changes are proposed to the Annex I, IIB and IIIB of the Comtess Product Information following the QRD template version 7.3. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data 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	22/04/2010	10/06/2010	SmPC, Annex II and PL	Following a request from the CHMP for entacapone-containing medicinal products, the product information has been updated with respect to ischemic heart disease events and myocardial infarction. Colitis is currently included in section 4.8 of the SPC. However, the MAH has now updated section 4.4 of the SPC following assessment of cumulative post-marketing safety data. Based on the new analysis, the colitis signal has not become more frequent nor increased in severity, but in order to provide additional information on the management of prolonged diarrhoea as a potential sign of colitis an update of section 4.4 is considered appropriate. The added sentence in section 4.4 states that prolonged or persistent diarrhoea appearing during use of entacapone may be a sign of colitis, and that in the event of prolonged or persistent diarrhoea, the drug should be discontinued and appropriate medical therapy and investigations considered. In addition, changes are proposed to the Annex I, IIB and IIIB of the Comtess product information following the QRD template version 7.3, and the PL has been revised following the results of a user test.
N/0042	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	05/08/2009	n/a	PL	
R/0037	Renewal of the marketing authorisation.	26/06/2008	03/09/2008	SmPC, Annex II, Labelling and PL	Based on the review of the available information the CHMP is of the opinion that the quality, the safety and the efficacy of this medicinal product continues to be adequately and sufficiently demonstrated and therefore considers that the

					benefit/risk profile of Comtess continues to be favourable. There is strong evidence on the positive causal relationship between impulse control disorders and antiparkinsonian therapy. However, whether these behaviours are simply related to dopaminergic medications or whether the primary pathological features of PD play a role is not known. The development of impulse control disorder has very often been linked to dopamine agonist administration, especially adjunctive agonist therapy combined with levodopa-carbidopa. Cumulatively, a total of three reports with pathological gambling and eight reports with libido increased or hypersexuality have been reported for entacapone. Based on this the CHMP endorsed the MAH proposal to include a a statement regarding the terms pathological gambling, libido increased and hypersexuality in sections 4.4 and 4.8 of the SPC of Comtess. A total of four reports including a reported overdose were received during the period (16 March 2006 to 16 January 2008) and one additional report of intentional overdose was received after the Data Lock Point (DLP). Of these five reports, three were identified as actual confirmed overdoses. Based on these cases the CHMP accepted the MAH suggested new wording of the Comtess SPC section 4.9 "Overdose" that would read as follows: "The post-marketing data includes isolated cases of overdose in which the reported highest daily dose of entacapone has been 16,000 mg. The acute symptoms and signs in these cases of overdose included confusion, decreased activity, somnolence, hypotonia, skin discolouration and urticaria."

IB/0039	IB_10_Minor change in the manufacturing process of the active substance	27/06/2008	n/a		
IB/0038	IB_10_Minor change in the manufacturing process of the active substance	27/06/2008	n/a		
IA/0041	IA_11_a_Change in batch size of active substance or intermediate - up to 10-fold	29/05/2008	n/a		
IA/0040	IA_11_a_Change in batch size of active substance or intermediate - up to 10-fold	29/05/2008	n/a		
IA/0036	IA_09_Deletion of manufacturing site	07/11/2007	n/a		
II/0034	This variation refers to an update of sections 4.4 and 4.8 of the Summary of Product Characteristics (SPC) and sections 2 and 4 of the Package Leaflet (PL) further to the assessment of the 10th PSUR (Periodic Safety Update Report). The MAH also took this opportunity to align the Product Information with the latest QRD templates and to update the list of contact details for the local representatives in the PL. Update of Summary of Product Characteristics, Labelling and Package Leaflet	24/01/2007	27/02/2007	SmPC, Annex II, Labelling and PL	During the 10th PSUR, cumulative information on 35 ADRs related to liver laboratory abnormalities or abnormal hepatic function in 29 reports had been reported. Of note, hepatitis, cytolytic hepatitis, hepatic failure, hepatotoxicity have been reported once, jaundice twice, liver disorder three times and cholestatic hepatitis four times. Cholecystitis and cholestatis have both been included in one report, and cholelithiasis in 3 reports. One case of cytolytic hepatitis preceding progressive asthenia, anorexia and loss of weight was reported with positive rechallenge. Therefore, the CHMP recommended the inclusion of a warning related to this safety concern in section 4.4 of the SPC and the inclusion of the terms "colitis" and "skin, hair, beard and nail discolorations" in section 4.8 of the SPC and relevant section of the PL. Within this type II variation, the MAH has reviewed post-marketing safety data and consequently analysed cumulative case reports of increased liver function tests associated with weight decrease,

					anorexia or asthenia. Additionally, the MAH provided an update of scientific literature regarding weight decrease in Parkinson's disease. Based on these data, section 4.4 of the SPC has been updated to reflect that "For patients who experience progressive anorexia, asthenia and weight decrease within a relatively short period of time, a general medical evaluation including liver function should be considered". "Colitis" and "skin, hair, beard and nail discolorations" were included in section 4.8 of the SPC and section 4 of the PL. Addition of a new subsection "Take special care with Comtess" for section 2 of the PL to include all the relevant precautions and warnings was also made.
II/0035	Update of or change(s) to the pharmaceutical documentation	24/01/2007	06/02/2007		
IA/0033	IA_12_a_Change in spec. of active subst./agent used in manuf. of active subst. - tightening of spec. IA_13_a_Change in test proc. for active substance - minor change	25/07/2006	n/a		
T/0031	Transfer of Marketing Authorisation	08/06/2006	11/07/2006	SmPC, Labelling and PL	
IA/0032	IA_47_a_Deletion of a pharmaceutical form	16/06/2006	n/a	SmPC, Labelling and PL	
IB/0030	IB_10_Minor change in the manufacturing process of the active substance	31/05/2006	n/a		
IA/0028	IA_36_ b_Change in shape or dimensions of the	24/05/2006	24/05/2006	SmPC,	

	container/closure - other pharm. forms IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size			Labelling and PL	
IA/0029	IA_11_a_Change in batch size of active substance or intermediate - up to 10-fold	18/05/2006	n/a		
II/0027	Quality changes	23/03/2006	27/04/2006	SmPC, Labelling and PL	
IA/0026	IA_12_a_Change in spec. of active subst./agent used in manuf. of active subst. - tightening of spec.	11/05/2005	n/a		
II/0025	The Marketing Authorisation Holder applied for changes to section 4.4 (Special warnings and special precautions for use) and section 4.8 (Undesirable effects) of the Summary of Product Characteristics to include information on neuroleptic malignant syndrome (NMS) and rhabdomyolysis following the assessment of the 8th PSUR. The Package Leaflet was revised accordingly. In addition, the MAH applied for the inclusion of typographical corrections to several language versions of the product information. Update of Summary of Product Characteristics, Labelling and Package Leaflet	20/01/2005	07/03/2005	SmPC, Labelling and PL	The MAH has closely monitored cases of NMS and rhabdomyolysis since the 5th PSUR and neuroleptic malignant syndrome (NMS) was mentioned in SPC section 4.4 warnings and precautions. NMS has been reported 9 times since market introduction of entacapone. In four out of nine of these cases entacapone and other PD drug treatment has been abruptly withdrawn 1-2 days before event onset. In the remaining cases many confounding factors could be recognized, severe underlying illnesses, complex drug treatments, and co-administration of entacapone with drugs reported to have been related to NMS even on their own, and these cases create no clear signal at the moment. The wording on NMS in section 4.4 of the SPC has been revised to state that isolated cases of NMS have been reported, especially following abrupt reduction or discontinuation of entacapone and other concomitant

					dopaminergic medications. It was also added to section 4.8 of the SPC that isolated cases of NMS have been reported following abrupt reduction or discontinuation of entacapone and other dopaminergic medications. This change was also reflected in the Package Leaflet.Since market introduction 9 cases of rhabdomyolysis have been reported to the MAH. Rhabdomyolysis has been mild or moderate and other possible causal factors have been detected. Consequently information has been added to section 4.8 of the SPC that isolated cases of rhabdomyolysis have been reported.
IA/0024	IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.)	24/02/2004	n/a		
R/0023	Renewal of the marketing authorisation.	24/07/2003	17/10/2003	SmPC, Annex II, Labelling and PL	
I/0022	26_Changes to comply with supplements to pharmacopoeias	02/05/2003	06/05/2003		
I/0021	25_Change in test procedures of the medicinal product	02/05/2003	06/05/2003		
II/0020	Update of Summary of Product Characteristics and Package Leaflet	27/06/2002	30/09/2002	SmPC and PL	
I/0017	12_Minor change of manufacturing process of the active substance	21/01/2002	06/03/2002		
I/0019	19_Change in specification of excipients in the medicinal product (excluding adjuvants for vaccines)	21/12/2001	07/01/2002		

I/0018	15_Minor changes in manufacture of the medicinal product 19_Change in specification of excipients in the medicinal product (excluding adjuvants for vaccines)	21/12/2001	07/01/2002		
I/0015	08_Change in the qualitative composition of immediate packaging material	24/10/2001	07/01/2002		
II/0011	Update of Summary of Product Characteristics	27/06/2001	24/10/2001	SmPC	
N/0014	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	14/09/2001	07/02/2002	PL	
I/0013	20a_Extension of shelf-life or retest period of the active substance	24/07/2001	n/a		
I/0012	12_Minor change of manufacturing process of the active substance	13/07/2001	n/a		
II/0010	Update of or change(s) to the pharmaceutical documentation	02/04/2001	02/05/2001		
II/0007	Update of Summary of Product Characteristics and Package Leaflet	11/04/2000	27/07/2000	SmPC, Labelling and PL	
N/0009	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	23/06/2000	n/a	PL	
I/0008	12_Minor change of manufacturing process of the active substance	20/01/2000	n/a		

II/0003	New safety warning	17/12/1998	18/05/1999	SmPC and PL	
N/0006	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	24/03/1999	11/05/1999	PL	
I/0005	31_Change in container shape	08/02/1999	n/a		
I/0004	13_Batch size of active substance	03/02/1999	n/a		
N/0002	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	13/11/1998	18/05/1999	Labelling and PL	
I/0001	12_Minor change of manufacturing process of the active substance 13_Batch size of active substance 12a_Change in specification of starting material/intermediate used in manuf. of the active substance	23/10/1998	n/a		