Stalevo

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/0102	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	12/12/2024		PL	
IG/1611/G	This was an application for a group of variations. B.III.1.a.2 - Submission of a new/updated or	18/05/2023	n/a		

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

	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				
IG/1580	A.7 - Administrative change - Deletion of manufacturing sites	12/01/2023	25/01/2024	Annex II and PL	
PSUSA/547/202110	Periodic Safety Update EU Single assessment - carbidopa / entacapone / levodopa	10/06/2022	n/a		PRAC Recommendation - maintenance
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	31/03/2022	n/a		

	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				
IG/1495	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	14/03/2022	n/a		
WS/2175	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	27/01/2022	23/01/2023	SmPC, Labelling and PL	
WS/2105/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.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.d.1.a.4 - Stability of AS - Change in the re-test	25/11/2021	n/a		

	period/storage period - Extension or introduction of a re-test period/storage period supported by real time data				
WS/2124/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.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.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)	16/09/2021	n/a		
IG/1408/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.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	17/06/2021	n/a		

	from an already approved manufacturer				
IG/1303	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	25/11/2020	09/12/2021	SmPC, Annex II, Labelling and PL	
N/0091	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	28/04/2020	09/12/2021	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		
WS/1667/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.	05/12/2019	n/a		

	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				
PSUSA/547/201810	Periodic Safety Update EU Single assessment - carbidopa / entacapone / levodopa	29/05/2019	31/07/2019	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/547/201810.
IG/1060	A.7 - Administrative change - Deletion of manufacturing sites	28/02/2019	n/a		
N/0086	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	18/12/2018	31/01/2019	PL	
IG/0965/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 the AS -replacement or addition of a site where	23/10/2018	n/a		

	batch control/testing takes place				
WS/1327	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	08/02/2018	31/01/2019	SmPC, Labelling and PL	
IG/0867	B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	20/11/2017	n/a		
IG/0858/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites 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	30/10/2017	n/a		
IG/0807	A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the	10/08/2017	n/a		

	finished product, including quality control sites (excluding manufacturer for batch release)				
PSUSA/547/201510	Periodic Safety Update EU Single assessment - carbidopa / entacapone / levodopa	13/05/2016	n/a		PRAC Recommendation - maintenance
N/0079	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	08/12/2015	25/01/2016	PL	
IG/0631/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.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.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	04/12/2015	n/a		

	deletion of Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer				
N/0077	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	27/05/2015	25/01/2016	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: - 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	22/01/2015	25/01/2016	SmPC, Labelling and PL	

	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				
WS/0651	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. To include an additional analytical method for the active substance carbidopa. 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	18/12/2014	n/a		To include an additional analytical method for the active substance carbidopa.
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 manufacturing site for the FP - Secondary packaging site	08/05/2014	n/a		
IG/0415/G	This was an application for a group of variations.	13/03/2014	n/a		

	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				
N/0071	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	14/08/2013	25/01/2016	PL	
IAIN/0070/G	This was an application for a group of variations. B.III.1.a.3 - Submission of a new or updated Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - New certificate from a new manufacturer (replacement or addition) B.III.1.a.2 - Submission of a new or updated Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer B.III.1.a.2 - Submission of a new or updated Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer B.III.1.a.2 - Submission of a new or updated Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting	13/05/2013	n/a		

	material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method				
IG/0302/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.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.III.1.a.2 - Submission of a new or updated Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer B.III.1.a.2 - Submission of a new or updated Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer B.III.1.a.2 - Submission of a new or updated Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer B.III.1.a.2 - Submission of a new or updated Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer 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	13/05/2013	n/a		

	corresponding test method				
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	14/01/2013	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.
IG/0229	B.III.1.a.3 - Submission of a new or updated Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - New certificate from a new manufacturer (replacement or addition)	09/11/2012	n/a		
IAIN/0066/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites B.III.1.a.3 - Submission of a new or updated Ph. Eur.	06/07/2012	n/a		

	Certificate of Suitability to the relevant Ph. Eur. Monograph - New certificate from a new manufacturer (replacement or addition) B.III.1.a.3 - Submission of a new or updated Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - New certificate from a new manufacturer (replacement or addition)				
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		
IG/0110	C.I.9.i - Changes to an existing pharmacovigilance system as described in the DDPS - Change(s) to a DDPS following the assessment of the same DDPS in relation to another medicinal product of the same MAH	04/10/2011	n/a		
X/0060	Annex I_2.(c) Change or addition of a new strength/potency	23/06/2011	24/08/2011	SmPC, Annex II, Labelling and PL	
IA/0062/G	This was an application for a group of variations. B.III.1.a.2 - Submission of a new or updated Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already	04/08/2011	n/a		

	approved manufacturer B.III.1.a.3 - Submission of a new or updated Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - New certificate from a new manufacturer (replacement or addition)				
IA/0061	B.III.1.a.3 - Submission of a new or updated Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - New certificate from a new manufacturer (replacement or addition)	18/04/2011	n/a		
IB/0059	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	18/01/2011	n/a		
II/0058	C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	22/07/2010	26/08/2010	SmPC and PL	The MAH has submitted a type II variation to update section 4.8 of the SPC. In the currently approved SPC, the adverse effect data are presented separately for entacapone and levodopa/carbidopa. In the new proposal for section 4.8, the data on adverse reactions are presented in a single table. The reporting frequencies of the adverse reactions have been updated according to all available clinical trial data (a total of 13 double-blind studies of which 11 studies included Parkinson's disease patients with wearing-off symptoms, and 2 studies included levodopa naive patients in early PD).
II/0056	To update the SPC section 4.4 and PL section 2 further to the signal of colitis. C.I.4 - Variations related to significant modifications	22/04/2010	02/06/2010	SmPC and PL	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

	of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				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 section 4.4 has been updated. The new warning 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. The PL has been updated accordingly.
IA/0057	B.III.1.a.2 - Submission of a new or updated Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer	15/04/2010	n/a		
II/0054	Update of sections 4.4 and 4.8 of the Summary of Product Characteristics (SPC) and relevant sections of the Package Leaflet (PL) with respect to ischemic heart disease events, myocardial infarction and irregular heart rhythm. In addition, yellow iron oxide has been deleted from section 6.1 of the SPC and section 6 of the PL for the Stalevo 75/18.75/200mg and 125/31.25/200mg strengths. Annex II has been updated to reflect a change in the PSUR cycle and other minor amendments have been introduced in the Product Information. Update of Summary of Product Characteristics and Package Leaflet	21/01/2010	23/03/2010	SmPC, Annex II and PL	The product information was updated to reflect that Stalevo therapy should be administered cautiously to patients with ischemic heart disease. In addition, the risk of heart attack (myocardial infarction) and the risk of heart or artery disease events other than a heart attack (e.g. chest pain) were added to the Product Information as possible side effects, classified as uncommon and common respectively. The incidence rates of myocardial infarction and other ischemic heart disease events (0.43% and 1.54%, respectively) are derived from an analysis of 13 double-blind studies involving 2082 patients with end-of-dose motor fluctuations receiving entacapone. Information on cardiac arrhythmias has been added to the SPC section 4.8, subtitle Levodopa/carbidopa, and irregular heart rate or rhythm has been added to the PL with frequency common.

					Yellow iron oxide has been deleted from relevant sections of the product information for Stalevo 75/18.75/200mg and 125/31.25/200mg since it is not used in these strengths.
IA/0055	IA_15_a_Submission of Ph. Eur. certificate for active substance - approved manufacturer	08/01/2010	n/a		
N/0053	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	05/08/2009	n/a	PL	
X/0046	Annex I_2.(c) Change or addition of a new strength/potency	22/01/2009	27/03/2009	SmPC, Annex II, Labelling and PL	This application for Stalevo 75/18.75/200 mg and 125/31.25/200 mg film-coated tablets is an extension application for the addition of two new dosage strengths to the existing Marketing Authorization for existing Stalevo 50/12.5/200 mg, 100/25/200 mg, 150/37.5/200 mg and 200/50/200 film-coated tablets. The new 75/18.75/200 mg and 125/31.25/200 mg strengths compare with the already marketed Stalevo strength with carbidopa and levodopa contained in 1:4 ratio and combined with 200 mg entacapone. In the fixed combination of three active ingredients, levodopa mediates the antiparkinsonian effect whereas carbidopa and entacapone inhibit the peripheral metabolism of levodopa. The indication is the same as for the other strengths, i.e. the treatment of Parkinson (PD) patients with end-of-dose motor fluctuations not stabilized with the combination of levodopa and dopa decarboxylase inhibitor. The new strengths being proposed are intermediates to the currently approved Stalevo tablets. The registration of the new Stalevo strengths is based on the strategy to develop incremental doses across the currently marketed Stalevo

					tablet strengths to enable more flexible dose titration of levodopa in clinical use. Separate bioequivalence studies have been conducted for the four approved strengths of Stalevo using Sinemet (levodopa/carbidopa) and Comtess (entacapone) as the corresponding reference products. In vitro dissolution approach has been used to establish equivalence for the two new Stalevo tablet strengths.
X/0045	Annex I_2.(c) Change or addition of a new strength/potency	22/01/2009	27/03/2009	SmPC, Annex II, Labelling and PL	This application for Stalevo 75/18.75/200 mg and 125/31.25/200 mg film-coated tablets is an extension application for the addition of two new dosage strengths to the existing Marketing Authorization for existing Stalevo 50/12.5/200 mg, 100/25/200 mg, 150/37.5/200 mg and 200/50/200 film-coated tablets. The new 75/18.75/200 mg and 125/31.25/200 mg strengths compare with the already marketed Stalevo strength with carbidopa and levodopa contained in 1:4 ratio and combined with 200 mg entacapone. In the fixed combination of three active ingredients, levodopa mediates the antiparkinsonian effect whereas carbidopa and entacapone inhibit the peripheral metabolism of levodopa. The indication is the same as for the other strengths, i.e. the treatment of Parkinson (PD) patients with end-of-dose motor fluctuations not stabilized with the combination of levodopa and dopa decarboxylase inhibitor. The new strengths being proposed are intermediates to the currently approved Stalevo tablets. The registration of the new Stalevo strengths is based on the strategy to develop incremental doses across the currently marketed Stalevo tablet strengths to enable more flexible dose titration of

					levodopa in clinical use. Separate bioequivalence studies have been conducted for the four approved strengths of Stalevo using Sinemet (levodopa/carbidopa) and Comtess (entacapone) as the corresponding reference products. In vitro dissolution approach has been used to establish equivalence for the two new Stalevo tablet strengths.
II/0051	Update of the section 4.8 the Summary of Product Characteristics to include angioedema as isolated cases reported after initiation of Stalevo on the basis of PSUR 7 data. Section 4 of the Package Leaflet was amended accordingly. Update of Summary of Product Characteristics and Package Leaflet	19/02/2009	19/03/2009	SmPC and PL	This update of the section 4.8 of the SPC is based on the cumulative data and information received during the period covered by PSUR 7. The following sentence has been added: "Isolated cases of angioedema have been reported after the initiation of Stalevo".
IA/0052	IA_08_a_Change in BR/QC testing - repl./add. of batch control/testing site	04/03/2009	n/a		
N/0048	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	17/12/2008	n/a	PL	
IA/0050	IA_15_a_Submission of Ph. Eur. certificate for active substance - approved manufacturer	08/12/2008	n/a		
IA/0049	IA_15_a_Submission of Ph. Eur. certificate for active substance - approved manufacturer	10/11/2008	n/a		
IA/0047	IA_15_b_02_Submission of Ph. Eur. certificate for active substance - new manuf./other substances	15/10/2008	n/a		

R/0040	Renewal of the marketing authorisation.	24/07/2008	15/09/2008	SmPC, Labelling and PL	
IB/0042	IB_10_Minor change in the manufacturing process of the active substance	27/06/2008	n/a		
IB/0041	IB_10_Minor change in the manufacturing process of the active substance	27/06/2008	n/a		
IA/0044	IA_11_a_Change in batch size of active substance or intermediate - up to 10-fold	29/05/2008	n/a		
IA/0043	IA_11_a_Change in batch size of active substance or intermediate - up to 10-fold	29/05/2008	n/a		
X/0033	Annex I_2.(c) Change or addition of a new strength/potency	21/02/2008	21/04/2008	SmPC, Labelling and PL	
II/0037	Quality changes	13/12/2007	19/12/2007		
IA/0038	IA_15_b_02_Submission of Ph. Eur. certificate for active substance - new manuf./other substances	11/10/2007	n/a		
II/0031	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 5th PSUR (Periodic Safety Update Report). The MAH also took the opportunity to align the Product Information with the latest QRD templates and to update the list of contact details of the local representatives in the PL.	19/07/2007	29/08/2007	SmPC, Labelling and PL	On the basis of the assessment of the 5th PSUR and the approved variations for entacapone products (Comtess EMEA/H/C/170/II/34 and Comtan EMEA/H/C/171/II/26), the CHMP recommended the inclusion of information related to colitis, discoloration of skin, hair, nail and beard; hepatitis and general medical evaluation including liver function for patients who experience progressive anorexia, asthenia and weight decrease into the relevant sections of

	Update of Summary of Product Characteristics, Labelling and Package Leaflet				the SPC and PL for Stalevo.
IB/0035	IB_33_Minor change in the manufacture of the finished product	03/08/2007	n/a		
IA/0036	IA_32_a_Change in batch size of the finished product - up to 10-fold	31/07/2007	n/a		
IA/0034	IA_29_b_Change in qual./quant. composition of immediate packaging - all other pharm. forms	31/07/2007	n/a		
IA/0032	IA_15_a_Submission of Ph. Eur. certificate for active substance - approved manufacturer	11/05/2007	n/a		
IA/0030	IA_15_a_Submission of Ph. Eur. certificate for active substance - approved manufacturer	23/03/2007	n/a		
IA/0029	IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size	26/02/2007	26/02/2007	SmPC, Labelling and PL	
IA/0028	IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size	26/02/2007	26/02/2007	SmPC, Labelling and PL	
IA/0027	IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size	26/02/2007	26/02/2007	SmPC, Labelling and PL	
II/0025	Update of Summary of Product Characteristics and Package Leaflet regarding pathological gambling,	14/12/2006	24/01/2007	SmPC, Annex II, Labelling	Following a review by the PhVWP/CHMP where pathological gambling and increased libido, including hypersexuality,

	increased libido, hypersexuality and overdose. Update of Summary of Product Characteristics, Labelling and Package Leaflet			and PL	had been suggested to be class effects of dopamine agonists the MAH updated the section 4.4 and 4.8 of the SPC and relevant section of the PL with these adverse reactions. In addition, following one case of overdose, the sentence "No case of overdose has been reported" was deleted from section 4.9 of the SPC. The MAH also took this opportunity to update the list of local representatives.
IB/0026	IB_33_Minor change in the manufacture of the finished product	11/01/2007	n/a		
IB/0024	IB_33_Minor change in the manufacture of the finished product	02/08/2006	n/a		
IB/0022	IB_33_Minor change in the manufacture of the finished product	02/08/2006	n/a		
IA/0023	IA_32_a_Change in batch size of the finished product - up to 10-fold	25/07/2006	n/a		
IA/0021	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/0020	Transfer of Marketing Authorisation	08/06/2006	11/07/2006	SmPC, Labelling and PL	
IB/0019	IB_33_Minor change in the manufacture of the finished product	21/04/2006	n/a		

	IB_31_b_Change to in-process tests/limits during manufacture - addition of new tests/limits				
IB/0018	IB_10_Minor change in the manufacturing process of the active substance	21/04/2006	n/a		
IA/0017	IA_11_a_Change in batch size of active substance or intermediate - up to 10-fold	06/04/2006	n/a		
IA/0016	IA_23_b_Change in source of excip./reagent to veg./synthetic material - other cases	06/04/2006	n/a		
IA/0015	IA_15_a_Submission of Ph. Eur. certificate for active substance - approved manufacturer	06/04/2006	n/a		
IA/0014	IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size	20/03/2006	20/03/2006	SmPC, Labelling and PL	
IA/0013	IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size	20/03/2006	20/03/2006	SmPC, Labelling and PL	
IA/0012	IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size	20/03/2006	20/03/2006	SmPC, Labelling and PL	
IA/0010	IA_15_a_Submission of Ph. Eur. certificate for active substance - approved manufacturer	17/11/2005	n/a		
IA/0009	IA_15_a_Submission of Ph. Eur. certificate for active substance - approved manufacturer	17/11/2005	n/a		

IA/0008	IA_15_a_Submission of Ph. Eur. certificate for active substance - approved manufacturer	17/11/2005	n/a		
II/0007	Update of Summary of Product Characteristics and Package Leaflet	27/07/2005	30/08/2005	SmPC and PL	Neuroleptic Malignant Syndrome (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 of entacapone 9 cases of rhabdomyolysis have been reported. 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.
II/0006	Following the assessment of the 2nd PSUR the Marketing Authorisation Holder applied for a revision	17/02/2005	29/03/2005	SmPC, Labelling and	A total of 35 reports including weight decrease and/or anorexia have been received since the first Marketing

	of the SPC section 4.8 to include the terms weight decrease and anorexia. MAH also added a warning in section 4.4 relating to possible weight decrease resulting from diarrhoea. The titles of the system organ classes are updated in the SPC, section 4.8 "Undesirable effects", under subtitle "Entacapone". The Labelling and Package Leaflet had been updated pursuant to Guideline on the excipients in the Label and Package Leaflet (CPMP/463/00). The Package Leaflet was updated accordingly. Update of Summary of Product Characteristics, Labelling and Package Leaflet			PL	Authorisation of entacapone. Weight decrease has been included altogether in 26 and anorexia in 15 reports, 6 reports included both Adverse Drug Reactions (ADRs). Most of the reports including weight decrease or anorexia included one or more additional ADRs. No clear pattern of adverse events was evident. Both weight loss and anorexia are often associated with other gastro-intestinal disorders and underlying medical conditions.The CHMP considered it appropriate to add the terms "anorexia" and "weight decrease" to section 4.8 of the Summary of Product Characteristics (SPC) and to include a warning regarding weight control in case of diarrhoea in section 4.4 for Stalevo.The Marketing Authorisation Holder also added a warning to section 4.4 of the SPC to state that Stalevo contains sucrose. In accordance with the guideline on excipients in the label and Package Leaflet of medicinal products for human use (CHMP/436/00) these changes were also reflected in the labelling and Package Leaflet.
IA/0005	IA_08_a_Change in BR/QC testing - repl./add. of batch control/testing site	11/11/2004	n/a		
N/0004	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	13/07/2004	n/a	PL	
IA/0003	IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.)	16/02/2004	n/a		
IA/0002	IA_15_b_02_Submission of Ph. Eur. certificate for active substance - new manuf./other substances	05/01/2004	n/a		

IA/0001	IA_15_b_02_Submission of Ph. Eur. certificate for active substance - new manuf./other substances	05/01/2004	n/a		